

Oxidative C-C Coupling Reactions of Benzofused Heterocycles Utilizing DDQ

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2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxidative coupling chemistry that was previously developed in the Floreancig group for coupling with chromene cations has been expanded to include other benzofused heterocycles, including benzoxathioles, and is described herein. The reactivity of these cationic intermediates was utilized to rapidly furnish coupled benzofused heterocycles. The reactivity of the cationic intermediates was explored via addition of a number of nucleophiles and the electronics of the substrate were altered to determine the scope of the substrate in this type of transformation. In addition a one-pot method was developed to access spiro compounds, in the orthoester oxidation state, containing a synthetic handle for further manipulation.

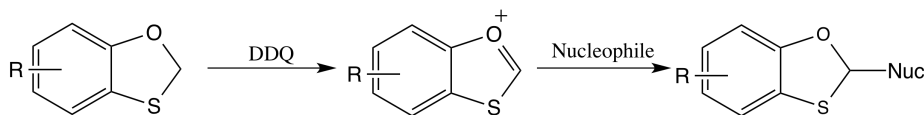


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LIST OF ABBREVIATIONS

| | |
|---------|--|
| 9-BBN | 9-Borabicyclo[3.3.1]nonane |
| C–C | Carbon–Carbon |
| C–H | Carbon–Hydrogen |
| C–N | Carbon–Nitrogen |
| COSY | Correlation Spectroscopy |
| DCE | 1,2-Dichloroethene |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL-H | Diisobutylaluminium hydride |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| IR | Infrared |
| LDA | Lithium diisopropyl amide |
| MPLC | Medium pressure liquid chromatography |
| NBS | N-Bromosuccinimide |
| NCS | N-Chlorosuccinimide |
| NMR | Nuclear magnetic resonance |
| Red-Al | Sodium bis(2-methoxyethoxy)aluminumhydride |
| TBAF | Tetra- <i>n</i> -butylammonium fluoride |

| | |
|-------|--------------------------------|
| TBS | <i>tert</i> -butydimethylsilyl |
| THF | Tetrahydrofuran |
| TIPS | Triisopyopysilyl |
| TMEDA | Tetramethylethylenediamine |
| TMS | Trimethylsilyl |

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1.0 C-H FUNCTIONALIZATION IN HETEROCYCLIC COMPOUNDS

Methods involving carbon-hydrogen bond functionalization to furnish carbon-carbon bonds have been studied with increasing frequency over the past 20 years.¹ These methods are attractive to chemists because they do not require the conversion of an unreactive starting material into an activated coupling partner, a necessary step in traditional metal-mediated cross couplings.^{2,3} Additionally, having a simple C-H bond as one of the coupling partners reduces the use of more activated compounds, which could be more difficult to handle. In a field that has growing emphasis on green methods this coupling technique, which is both atom and step economical, is an attractive area for study.^{4,5} Carbon-hydrogen bond activation has been utilized in a number of total syntheses of biologically viable molecules as well as method development projects.⁶ There are various methods that are available for this type of coupling, but the contents of this document will mainly focus on the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, which will be referred to from now on as DDQ (Figure 1.1).⁷

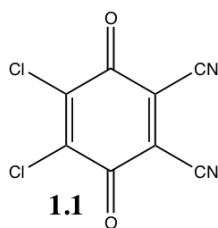
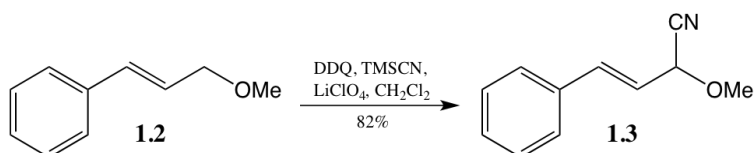


Figure 1.1 Structure of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

1.1 OXIDATIVE C-H BOND FUNCTIONALIZATION AND CROSS COUPLING

1.1.1 Functionalization of C-H Bonds Utilizing DDQ

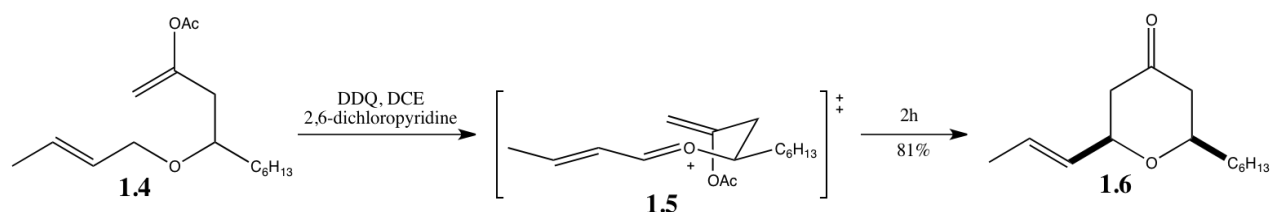
The most common example of DDQ mediated C-H bond functionalization is para-methoxybenzyl ether cleavage, in which oxidative cleavage is promoted via the electron rich arene stabilizing the developing cation intermediate through its π -orbitals.⁸ Mukaiyama and co-workers were able to expand the applications of this technique in 1987 and employ DDQ in an oxidative coupling procedure to form C-C bonds (Scheme 1.1).⁹ In this seminal work they used DDQ to form the target cationic intermediate of a number of ethers which were then subjected to various silyl nucleophiles. Loupy and co-workers later found that addition of LiClO_4 to the reaction mixture increased the yields of these reactions by forming a more reactive ion pair with



Scheme 1.1 Mukaiyama Oxidative Formation of C-C Bonds

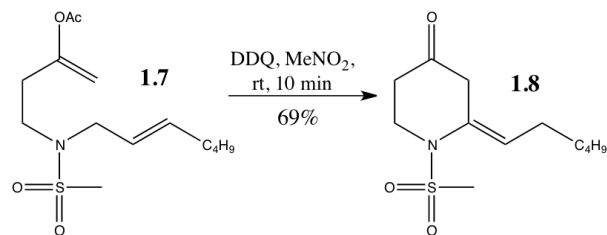
the resulting cation by disrupting the formation of a non-reactive DDQ adduct.¹⁰ Additionally, they found that if the nucleophile was added after the reactive oxocarbenium intermediate was formed, the yield increased. The presence of the cation intermediate throughout the course of the reaction is very telling of its stability, which unfortunately initially limited the scope of viable nucleophiles and general reactivity. Mukaiyama and co-workers' publication set the stage for what would become a multitude of reported C-H functionalization methods utilizing DDQ.

The Floreancig group has extensive experience in oxidative cation formation and sought to establish new methods utilizing DDQ as the oxidant. Their first attempts were to expand the scope of the reaction to stereoselective ring formation by showing that they can oxidize target compounds using DDQ and react them with various tethered nucleophiles.¹¹ This method was shown to cyclize allylic ether **1.4** to yield tetrahydropyrone **1.6** with good tolerance to various functional groups present and with excellent diastereocontrol (Scheme 1.2). The observed diastereocontrol was attributed to a chair transition state **1.5**, shown below, and the products of this reaction exhibited a 2,6-*cis* relationship of the ring substituents. The chair transition state model was later used to develop the key step in the synthesis of the neopeltolide macrocycle and its analogs.¹² Further studies by Liu concluded that the diastereoselectivity was decreased when



Scheme 1.2 DDQ Mediated Formation of Tetrahydropyrones

propargyl ethers were used in the reaction protocol, which was ultimately attributed to the decreased steric demand of alkynes versus alkenes.¹³ The decreased rigidity in the transition state of these types of molecules was exploited in the synthesis of the four diastereomers of 2,6-substituted-tetrahydropyran-4-ols. The Floreancig group has also reported methods by which oxidation and cyclization of enamides, *N*-vinyl sulfonamides, and vinyl sulfides can form piperidines and sulfur containing heterocycles (Scheme 1.3).^{14,15}



Scheme 1.3 DDQ Mediated Ring Closure of N-Vinyl Sulfonamide Species

Developing methodology for oxidative coupling is not the only area addressed by the Floreancig group. Dr. Jung has studied the mechanism by which DDQ oxidizes ethers and hypothesized the pathway by which DDQ acts (Figure 1.2).¹⁶ Using the kinetic isotope effect, Dr. Jung discovered that there is a quick electron transfer that occurs between the benzylic ether and DDQ. This transfer yields radical cation **1.10**, which then undergoes a hydrogen atom abstraction or a proton transfer followed by another electron transfer to generate oxocarbenium ion **1.12**. The results of this mechanistic study also showed that hydrogen removal from the radical cation is the rate-determining step in these reactions. Ultimately Dr. Jung was able to provide a strong defense for the idea that these reactions follow an electron transfer mechanism versus a hydride transfer mechanism.

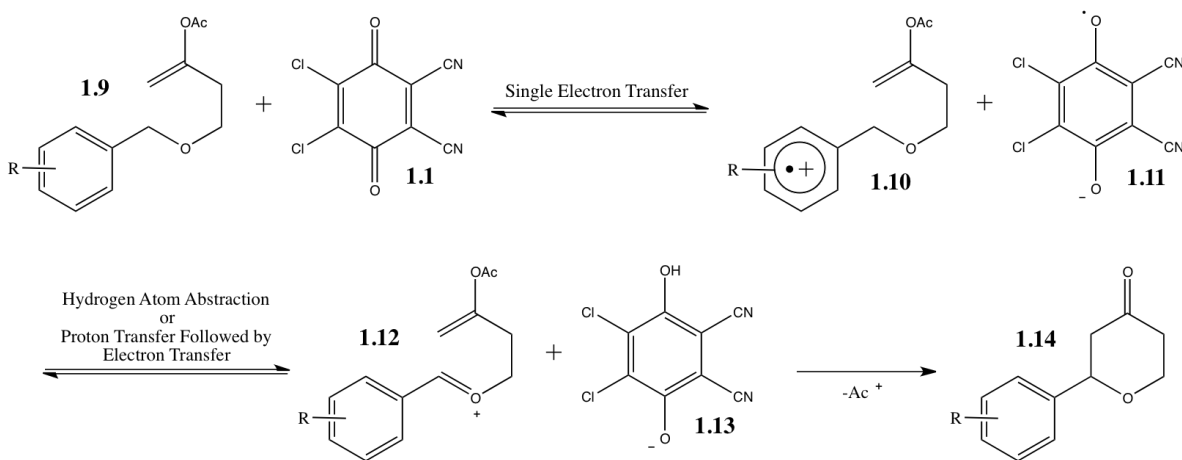
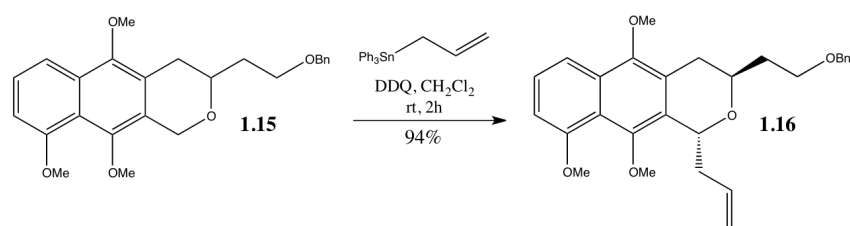


Figure 1.2 Proposed Mechanism of DDQ Oxidation

1.1.2 Oxidative Cross Coupling

Exploration of the potential applications of DDQ outside the realm of cyclization reactions led researchers to pursue techniques that employ DDQ in bimolecular coupling reactions. Bimolecular reactions are an important class of reactions that allow for convergent syntheses and are good for preparing diverse libraries of compounds. A number of methods involving the reaction of nucleophiles with cations formed via oxidative bond cleavage have been developed and the rise of these reactions has opened many new synthetic pathways.¹⁷ The common thread in each of these different oxidative coupling techniques is the formation of a persistent yet reactive cation. Stability of the cation is important to avoid decomposition under the reaction conditions and it must be in balance with its reactivity in order for it to undergo successful bimolecular coupling.

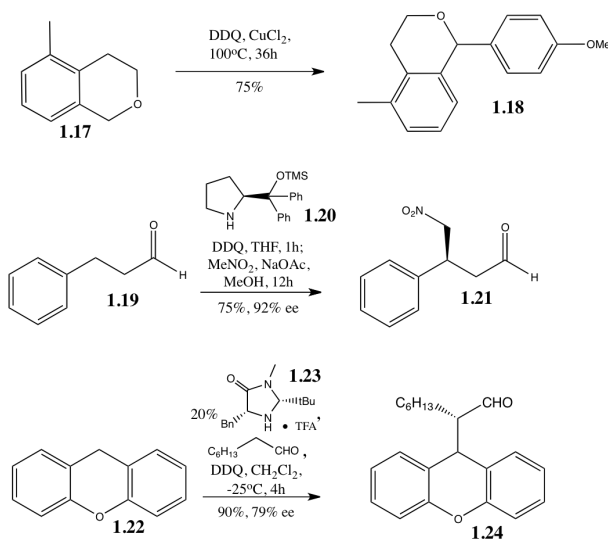
Balance of the two aforementioned criteria was achieved by a number of different groups through development of methods based on a specific type of substrate. Xu and co-workers were able to expand on Mukaiyama's DDQ oxidation chemistry and apply it to isochroman substrates in dichloromethane with various nucleophiles. Using this technique they were able to synthesize a number of isochroman derivatives in good yields.¹⁸ High *trans* selectivity was observed in the 3-substituted substrates and this chemistry was eventually applied in the total synthesis of deoxyfrenolicin **1.16** (Scheme 1.4).²³ They were then able to broaden the scope of the method to



Scheme 1.4 DDQ Oxidative Allylation Using Triphenyl Tin Nucleophile to Synthesize Deoxyfrenolicin

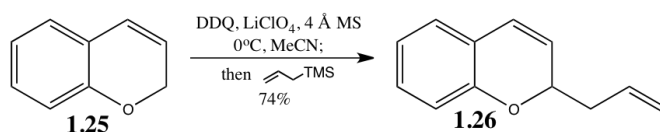
include acyclic benzyl ethers containing electron rich arenes¹⁹, however the unactivated species formed no desired product. Xu attributes this observation to encouragement of the initial hydrogen abstraction by the stability of the cationic intermediate, promoted by the electron donating ability of the arenes.

Additional coupling methods utilizing DDQ have been explored in a number of different systems (Scheme 1.5). Li developed a cross-dehydrogenative method to affect successful coupling between simple benzyl ethers and ketones that were previously found to be unreactive in metal mediated procedures. Park and co-workers demonstrated that isochroman **1.17**, after DDQ oxidation, would undergo a Friedel-Crafts addition onto anisole to form compounds like **1.18**.²⁰ Hayashi and co-workers have also developed an asymmetric variant of these types of couplings. First they formed chiral enamine compounds with the aid of an organocatalyst derived from proline, compound **1.20**.²¹ DDQ oxidized the enamine to an iminium ion followed by a stereospecific attack by nitromethane to afford **1.21**. Cozzi et al published another asymmetric variant, where addition into the cation was by a chiral enamine, obtained via a dehydration of an aldehyde by an organocatalyst **1.23**.²²



Scheme 1.5 Selected Oxidative Cross Coupling Reactions

A recent publication out of the Floreancig group by Dr. Clausen outlines a method that can be utilized to form a number of 2H-chromene derivatives (Scheme 1.6).²⁴ The process takes advantage of the aromaticity of the carbocation to stabilize the oxocarbenium intermediate and



Scheme 1.6 DDQ Oxidative Cross Coupling of 2-H Chromene and Allyl Silane Nucleophile

subsequently they found that there was a tolerance to both electron withdrawing and electron donating groups on the 2H-chromene starting materials. Using this method they were able to affect coupling between 2H-chromene and weakly nucleophilic potassium trifluoroborates and prochiral allylsilanes. They were also able to establish a transition state model for the addition of prochiral allylsilane nucleophiles (Figure 1.3). Functionalization of the pyran unit of the

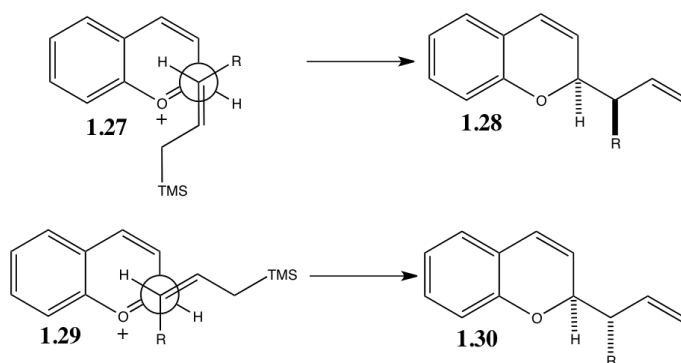


Figure 1.3 Transition State Model of Prochiral Allyl Silanes

2H-chromene with a silyl group further expanded the scope of this method by providing an additional synthetic handle from which to synthesize numerous derivatives. The effect of the aromatic cation intermediate was also studied and reaction rates were compared to a similar substrate where the reaction did not proceed through an aromatic intermediate. Dr. Clausen found that the rate of the reaction was greatly increased in the case where an aromatic cation was formed, with observed reductions in reaction times from 24 hours at room temperature to 10 minutes at -30°C.

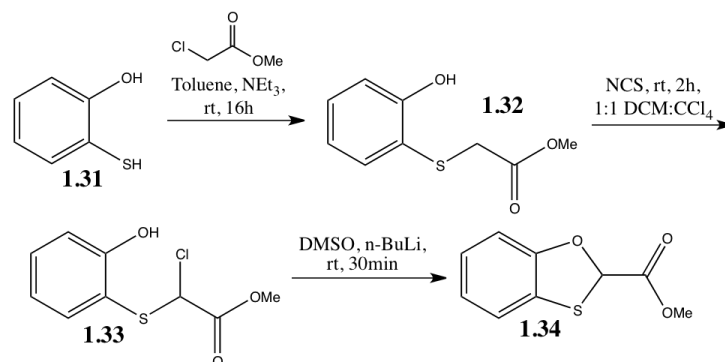
1.2 PREVIOUS SYNTHESSES OF C-2 FUNCTIONALIZED BENZOFUSED HETEROCYCLES

1.2.1 Previously developed methods

Synthesis of benzannulated 1,3-diheteroatom five-membered rings is an attractive area for study because of their medicinal and industrial use.²⁵ Typically these structures are synthesized through condensation of 1,2-disubstituted benzenes with aldehydes or ketones in the presence of an acid catalyst.²⁶ These conditions however are usually harsh and tend to be limited in pre-existing functionality of the aldehyde or ketone. The reactions typically involve a strong dehydrating agent, reagents that require close monitoring like LDA, or tedious workups due to the presence of multiple equivalents of acid.

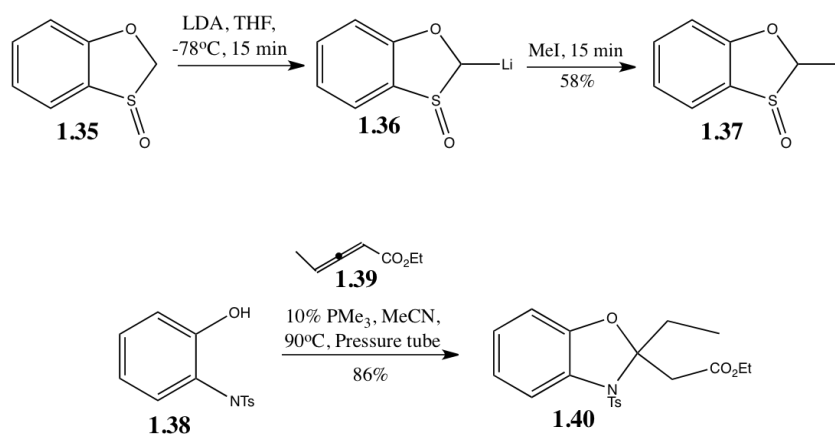
D'Archangelis and Cowan (Scheme 1.7) found that they could form the C-2 substituted benzoxathiole via a three-step procedure where they first synthesize ester **1.32**, which they could

then functionalize to **1.33** using NCS. From here the five membered ring was formed via an intramolecular Williamson ether synthesis which furnished the final product **1.34**.²⁷ Cabbidu



Scheme 1.7 D'Archangelis and Cowan's Synthesis of C-2 Ester Substituted 1,3-Benzoxathiole

and co-workers have a number of publications where they used LDA to metallate the benzannulated substrate **1.35** to form nucleophilic intermediate **1.36** after which they added an electrophile to generate C-2 coupled product **1.37** (Scheme 1.8).²⁸ This method produced undesirably low yields and was relatively limited in electrophile scope. Szeto and co-workers developed an alternative method by which to form C-2 di-substituted systems that involved a base catalyzed double-Michael addition of a 1,2 substituted benzene **1.38** into allene **1.39** to provide disubstituted product **1.40**.²⁹



Scheme 1.8 Additional Methods to Synthesize C-2 Substituted Benzannulated 5-Membered Rings

So while there has been exploration into this area, there is still room for further development. We sought to add a new method to synthesize these C-2 substituted products by applying the DDQ coupling chemistry that has been developed in our lab. Specifically we sought to expand on the developments in oxidative coupling procedures using 2-H chromene, mentioned above. Our aim was to provide a more step and atom economical method to furnish these C-2 substituted benzannulated 5 membered ring systems in higher yields, utilizing more benign reaction conditions.

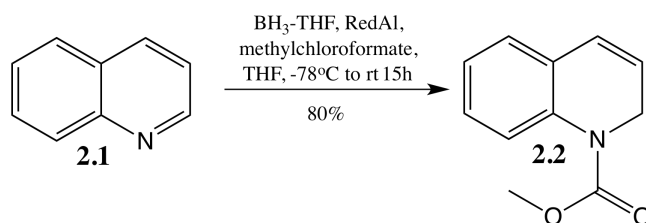
2.0 OXIDATIVE COUPLING REACTION IN HETEROCYCLIC COMPOUNDS

The Floreancig group has previously shown that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) can be used in the formation of heterocycles. We have established an intramolecular method for the oxidative coupling of allylic or benzylic ethers and tethered nucleophiles.¹¹ Intermolecular methods have also been explored and developments have been made in forming substituted benzopyrans.¹³ Recently, publications from the group have expanded this intermolecular route to include C-C bond formation with heterocyclic compounds and various nucleophiles.²⁴ We hypothesized that we could expand further on this chemistry to include oxidative additions to N-heterocyclic compounds and heterocyclic compounds containing more than one heteroatom.

2.1 INITIAL WORK

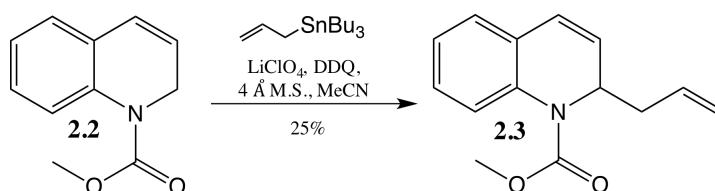
2.1.1 Quinoline Derived Heterocycles

This project started as a direct variant on the chemistry developed by Dr. Clausen, with the goal being to expand the method to dihydroquinoline derivatives. We initially prepared methyl quinoline-1(2*H*)-carboxylate **2.2** by subjecting quinoline to BH₃-THF and Red-Al then adding methyl chloroformate (Scheme 2.1).³⁰ Once we had **2.2** in hand we subjected it to 1.5



Scheme 2.1 Formation of Quinoline Derivatives

equivalents of DDQ in acetonitrile with 3.0 equivalents of 2,6-dichloropyridine and 1.5 equivalents of LiClO_4 to furnish the cation, then we added 2.0 equivalents of allyl tributylstannane.²⁴ Our initial attempts failed and we adjusted a number of the conditions until we were finally able to effect successful coupling (Scheme 2.2) between the substrate and allyl tributylstannane to form **2.3**, however the yield was a low 25%. The carbonyl carbon proved



Scheme 2.2 Coupling Of Carbamate Substrate and Allyl Tributylstannane Nucleophile

to be a more potent electrophile and in every case we observed a significant amount of side product formation resulting from cleavage of the carbonyl C-N bond, furnishing the acylated nucleophile and the original quinoline. We attributed this preferred pathway to the stability of the cation intermediate, which we were able to isolate and observe via NMR.

We thought that by crowding the immediate area around the carbonyl we would be able to block nucleophilic attack and force more reactivity at the desired position. We prepared a number of quinoline-based compounds, with increased steric bulk around the carbonyl, using the above-mentioned conditions and the appropriate chloroformates to form the N-substituted derivatives shown below (Figure 2.1).³⁰ We were unsuccessful in promoting coupling as the

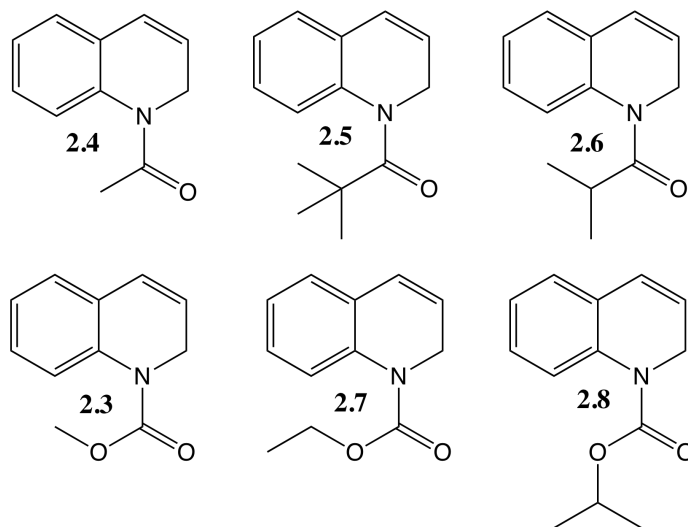


Figure 2.1 Quinoline Derivatives

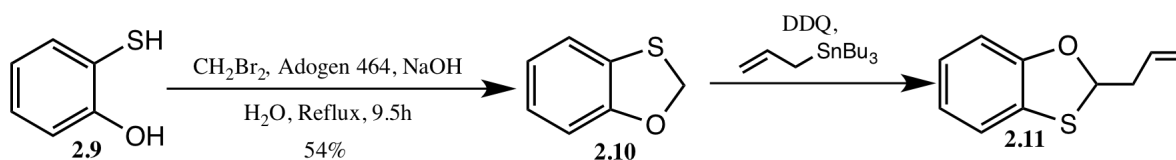
favorable reaction and attempted to further increase the steric bulk around the carbonyl by eliminating the oxygen. We synthesized three N-acyl species derived from acyl (**2.4**), isobutyryl (**2.5**), and pivaloyl (**2.6**) chloride but we were ultimately unsuccessful in our attempts. We were in most cases able to furnish a small amount of our desired product but in the end it was just not the pathway that was favored.

We then decided to move in a new direction with this method and attempt to apply it to heterocycles containing multiple heteroatoms. Substituted, di-heteroatom containing heterocycles are a good area for study because of their presence in medically relevant compounds and their utility in an industrial setting.²⁵ We planned to synthesize these types of substituted compounds in a different manner than has been previously reported. There are examples of using the anionic form of the heterocycle as a nucleophile in the C-C bond formation, as well as cyclization reactions on substituted methylene units.^{28,29} Our aim was to access these compounds through coupling of a cationic intermediate, obtained via DDQ

oxidation of the heterocycle, and a non-tethered nucleophile. Using this method, it was our hope that we would be able to provide a more step and atom economical method by which to synthesize these derivatives as well as expand the scope of the heterocyclic systems that can undergo this transformation.

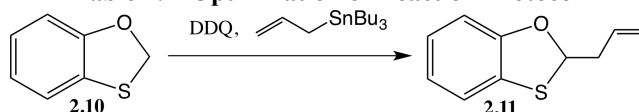
2.2 REACTION OPTIMIZATION

We decided to use benzo[*d*][1,3]oxathiole in the model reaction to optimize our coupling process. Benzo[*d*][1,3]oxathiole **2.10** is accessed from 2-mercaptophenol **2.9** in the presence of base via a one-step method involving dibromomethane and phase transfer catalyst Adogen 464 (Scheme 2.3).³¹ With the benzoxathiole in hand we sought to develop a coupling protocol utilizing the model reaction depicted below (Scheme 2.3), to yield compound **2.11**. We began to



Scheme 2.3 Preparation of Benzo[*d*][1,3]oxathiole and Model Coupling Reaction

test a number of reaction parameters before discovering the optimized conditions (Table 2.1). We found that ether and DCM were acceptable solvents in which to run these reactions, providing us with modest yields, 50-70%, but by changing to 1,2-dichloroethane we were able to increase the yields to 60-90%. These reactions were also found to proceed in THF but with a

Table 2.1 Optimization of Reaction Protocol

| Solvent | DDQ | LiClO ₄ | Nucleophile | Mol. Sieves | Yield |
|-------------------|------------------|--------------------|------------------|-------------|------------------|
| THF | 1.0 equiv | N/A | 1.5 equiv | No | 10% |
| DCM | 1.0 equiv | N/A | 1.5 equiv | No | 30% |
| Et ₂ O | 1.0 equiv | N/A | 1.5 equiv | No | 27% |
| MeCN | 1.0 equiv | N/A | 1.5 equiv | No | 0% |
| Toluene | 1.0 equiv | N/A | 1.5 equiv | No | 0% |
| DCM | 1.0 equiv | 1.5 equiv | 1.5 equiv | Yes | 58% |
| Et ₂ O | 1.0 equiv | 1.5 equiv | 1.5 equiv | Yes | 32% |
| DCM | 1.2 equiv | 1.5 equiv | 1.5 equiv | Yes | 64% |
| Et ₂ O | 1.2 equiv | 1.5 equiv | 1.5 equiv | Yes | 40% |
| DCM | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 66% |
| Et ₂ O | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 44% |
| DCM | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 80% ^a |
| Et ₂ O | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 75% ^a |
| 1,2 DCE | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 90% ^a |
| THF | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 10% ^a |
| Toluene | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 0% ^a |
| Nitromethane | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 0% ^a |
| DMF | 1.2 equiv | 1.5 equiv | 1.2 equiv | Yes | 0% ^a |

All reactions were run at room temperature. Reaction mixtures were purified without workup. ^aReactions were stirred with DDQ for 30 minutes prior to nucleophile addition.

large reduction in overall yield due to difficulty in oxidizing to the cation. We next addressed the amount of DDQ needed in the reaction and found that 1.2 equivalents would nicely form the reactive oxocarbenium intermediate in less than 30 minutes at room temperature. The 1,2-dichloroethane was stored on molecular sieves and 4 Å molecular sieves were added to the reaction mixture to prevent water from entering and quenching the reactive intermediate and forming undesired dimerization products. LiClO₄ was added to break up the DDQ adduct that formed and create a stable, reactive ion pair with the oxocarbenium intermediate.¹⁰ Finally we

varied the amount of nucleophile that was added and found that 1.2 equivalents was optimum and that by adding the nucleophiles after the reactive intermediate was formed we saw higher yields.

The reaction of the substrate with DDQ was hypothesized to proceed via the mechanism outlined in Figure 2.2. The radical cation intermediate **2.12** was formed via the addition of DDQ to our substrate **2.10** after which it underwent either a hydrogen atom abstraction or a proton transfer followed by an electron transfer to furnish cation **2.13**. The formation of unreactive DDQ adduct **2.14**, between cation **2.13** and DDQH⁻ **1.13**, was disrupted by the presence of LiClO₄, which formed the reactive ion pair **2.15**. Finally the π -nucleophile was added which furnished final C-C coupled product **2.16** in good yields.¹⁶

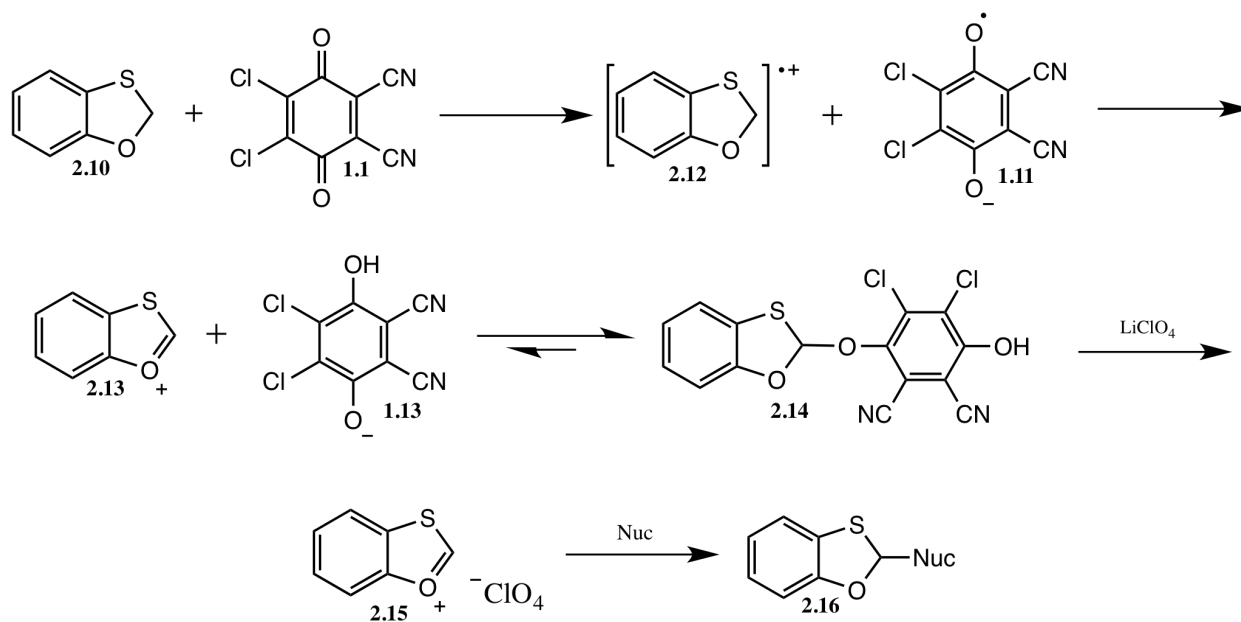
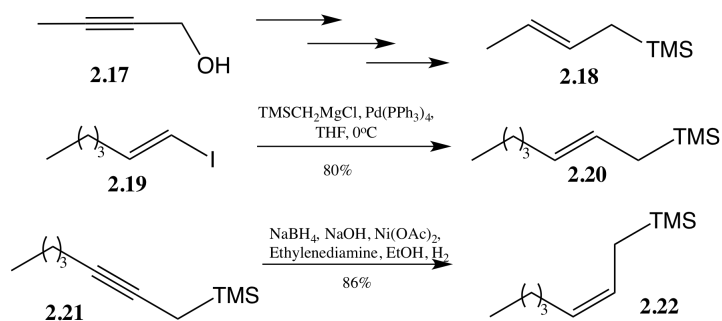


Figure 2.2 Proposed Pathway of DDQ Coupling Reaction with Benzo[d][1,3]oxathiole

2.3 NUCLEOPHILE SCOPE

2.3.1 Selection and Synthesis of Nucleophiles

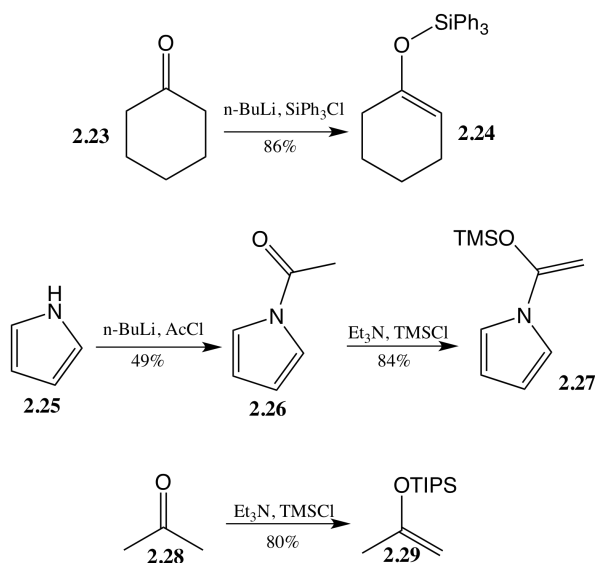
Once we had obtained an optimized reaction protocol for the coupling, we set out to select and synthesize various π -nucleophiles to test with our substrate. We first chose a number of representative allyl silanes to use in our reaction conditions, some of which were commercially available and some we needed to prepare. Allyl trimethylsilane and methallyl trimethylsilane were both purchased directly from Aldrich as was the allyl tributyl stannane. The (*E*)-Crotyl trimethylsilane **2.18** was synthesized previously by a member of the Floreancig group via a method developed in house starting from propargyl alcohol **2.17**.²⁴ *Trans* olefin **2.20** was synthesized from vinyl iodide **2.19** and trimethylsilyl methyl Grignard reagent using a palladium mediated Kumada coupling protocol.³² The *cis* isomer **2.22** of the same compound was obtained from propargylic alkyne **2.21** via a P-2 nickel reduction.³³



Scheme 2.4 Synthesis of Allylsilanes

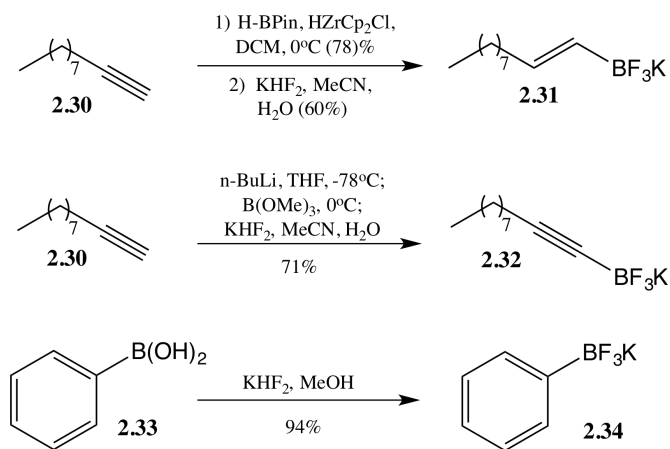
We also gathered a number of silyl enol ethers, which are shown in Scheme 2.5 below. Triphenylsilyl enol ether **2.24** was obtained from the reaction of cyclohexanone **2.23** with triethyl amine and triphenylsilyl chloride.³⁴ The pyrrole containing enol ether **2.27** was

synthesized via an N-acylation of pyrrole **2.26** with acetyl chloride followed by standard enol ether formation utilizing triethylamine and TMSCl.³⁵ The same enol forming conditions used to furnish **2.27** were also used to prepare acetone derived enol ether **2.29**.



Scheme 2.5 Preparation of Silyl Enol Ether Nucleophiles

The third class of compounds that we assessed was potassium trifluoroborates (Scheme 2.6).³⁶ MacMillan and co-workers has demonstrated success using these types of nucleophiles with iminium ions³⁷ and Dr. Clausen in our group was able to effect coupling with these and benzopyran compounds.²⁴ 1-Decyne (**2.30**) derived organotrifluoroborates were what we primarily used in our testing protocol. 1-Decyne (**2.30**) was reduced to a *trans*-1,2-disubstituted vinyl borane using pinacolborane with a catalytic amount of Schwartz reagent.³⁸ The borane was then converted to the desired vinyl organotrifluoroborate salt **2.31** using aqueous potassium bifluoride (KHF₂). Alkynyl trifluoroborate **2.32** was synthesized by exposing 1-decyne to n-BuLi and the resulting anion was quenched with KHF₂.³⁹ Phenyl boronic acid **2.33** and KHF₂ were combined in methanol to furnish potassium phenyl trifluoroborate **2.34**.²⁴



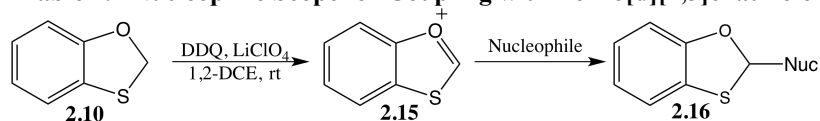
Scheme 2.6 Synthesis of Potassium Trifluoroborate Nucleophiles

2.3.2 Testing Nucleophile Scope in the Coupling Protocol

The scope of the nucleophiles is outlined below in Table 2.2. We tested each nucleophile within our optimized oxidation protocol with variations in reaction time of the nucleophile, noted in the table. There was no workup after the addition was complete; the reaction was purified directly via flash chromatography and the isolated yields are reported.

The highest yielding reaction was between our substrate and allyl tributyl stannane to afford compound **2.11** in 90% yield within 30 minutes. Allyl trimethylsilane afforded the identical coupled product in the same time frame but with a 79% yield. We next moved to the bulkier allylsilane nucleophiles and tested the olefin isomers **2.18** and **2.20**. In addition to increased reaction times required for the coupling to reach completion (4h) we noted moderate diastereocontrol in the addition of these olefins. The addition of the *trans*-olefin exhibited 3.1:1 ratio of diastereomers and the *cis*-olefin addition had even higher control with a 1:4.6

Table 2.2 Nucleophile Scope for Coupling with Benzo[d][1,3]oxathiole



| Nucleophile | Product | Yield |
|-------------|-------------|------------------------------|
| 2.35 | 2.11 | 90% |
| 2.36 | 2.11 | 79% |
| 2.18 | 2.38 | 74% 3.2:1 dr |
| 2.20 | 2.39 | 72% ^a 3.1:1 dr |
| 2.22 | 2.40 | 66% ^a 1:4.6 dr |
| 2.27 | 2.41 | 44% ^a |
| 2.24 | 2.42 | 75% 1.2:1 dr |
| 2.29 | 2.43 | 27% |
| 2.32 | 2.44 | 65% |
| 2.31 | 2.45 | 55% ^a |
| 2.37 | 2.46 | 61% 2:1 E:Z |
| 2.34 | 2.47 | 0% |

All reactions were run in 1,2-DCE at rt with LiClO₄ (1.5 equiv.) and DDQ (1.2 equiv.). Reactions were stirred for 30 minutes prior to adding the nucleophile (1.2 equiv.). Reaction mixtures were purified after stirring an additional hour. ^aReactions were stirred 4 hours.

diastomeric ratio in favor of the opposite diastereomer. The product from coupling with the (E)-crotyl trimethylsilane **2.18** also exhibited diastereocontrol with a 3.2:1 dr.

The enol silanes were the next group of nucleophiles we tested and we were able to use the triphenyl silyl enol ether **2.24** to determine the diastereocontrol for nucleophilic addition into the cation. We found that, in this case, the nucleophile delivery occurred with a 1:1.2 dr. The acetone derived enol silane **2.29** added to form expected product **2.43** and TLC of this reaction looked similar to any other addition but upon purification it was found that the yield was greatly diminished. This is probably due to a retro aldol-like reaction occurring after coupling takes place. The TMS enolate of N-Acetyl pyrrole **2.27** afforded a unique result that was unlike the previous enol silanes. The coupling of this nucleophile with our substrate resulted in the electrophilic aromatic substitution product **2.41** as opposed to the expected enolate addition product. Using COSY we determined that the addition was taking place on the 2-position of the pyrrole ring.

The final group of π -nucleophiles that we tested was potassium organotrifluoroborates. We were able to achieve successful coupling with a majority of these weak nucleophiles within our system. Alkynyl trifluoroborate **2.32** and 1,2-disubstituted vinyl trifluoroborate **2.31** both coupled in the expected manner with decent yields, 63% and 50% respectively. The 1,1-disubstituted vinyl trifluoroborate **2.37** underwent a rearrangement to form allyl coupling product **2.46** in a 2:1 olefin mixture. Potassium phenyl trifluoroborate **2.34** was completely unreactive under these conditions and provided no desired product formation even after heating and stirring for several days, indicating that the TMS enolate **2.26** creates a sufficiently electron rich ring whereas trifluoroborate does not.

2.3.3 Spiro Ring Formation and a One-Pot Method

Our initial attempts at forming spiro systems using this chemistry involved one-pot formation of spiro benzopyran **2.53**. Our plan was to first prepare compound **2.48**, from which we could then use our oxidative procedure to form spiro compound **2.53** in one step with DDQ (Figure 2.3).

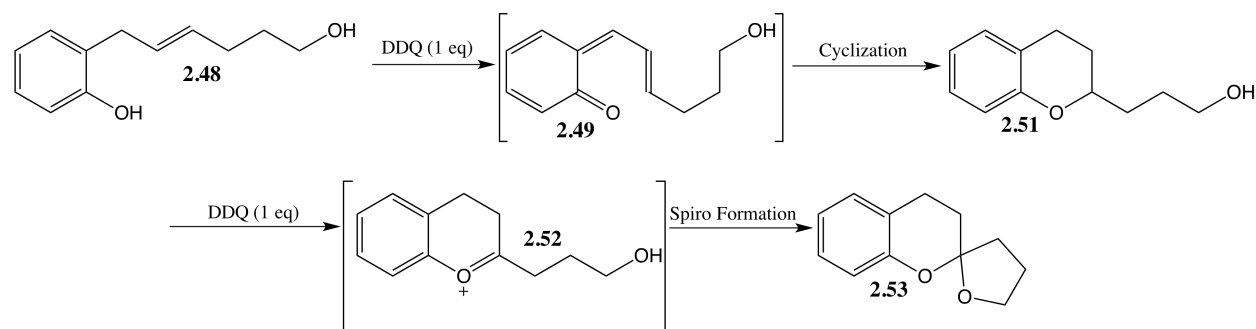
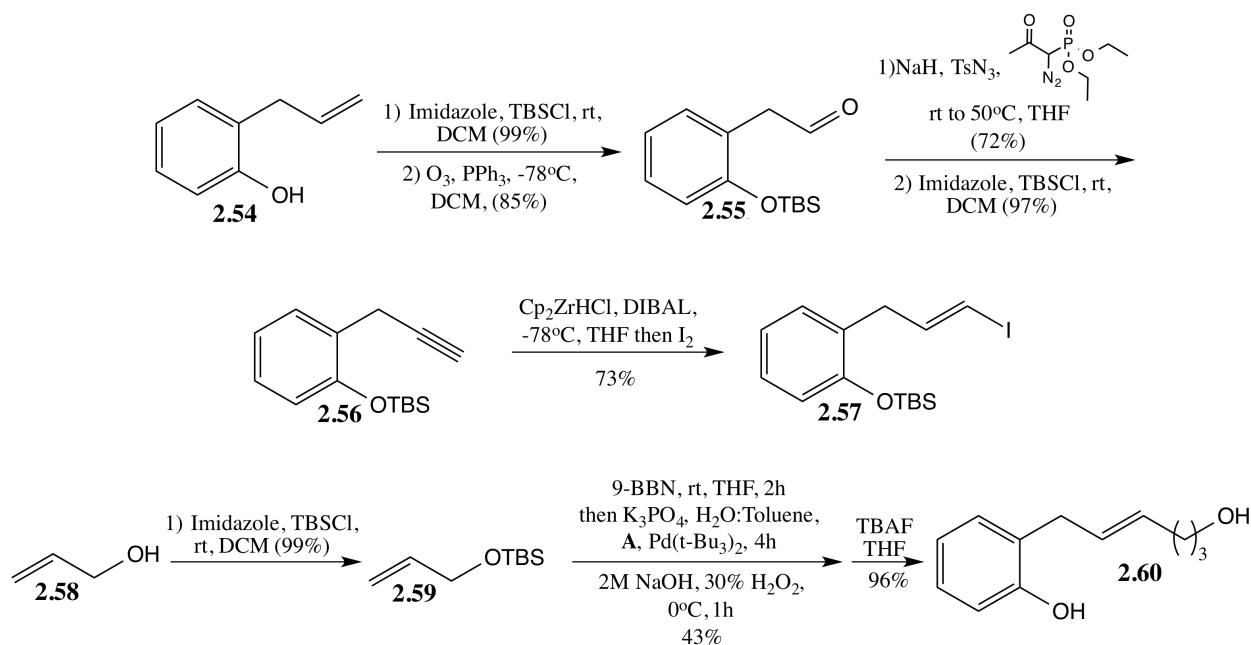


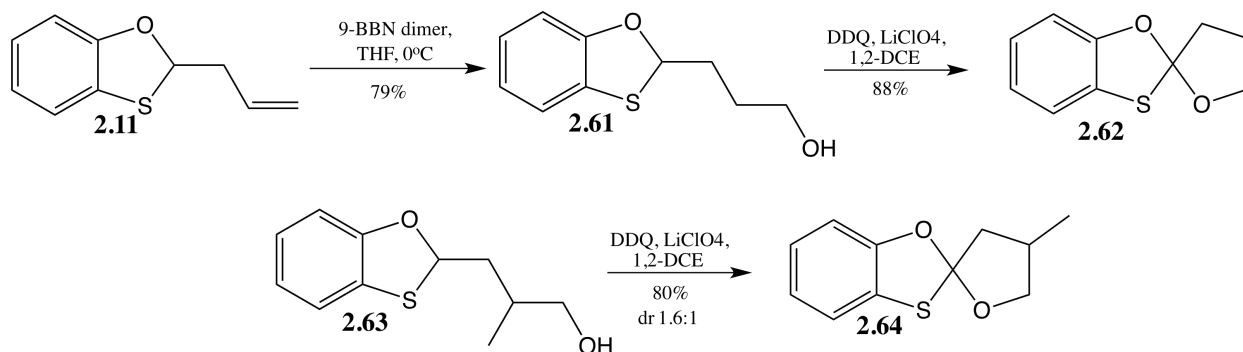
Figure 2.3 Proposed Spiro 2-H Chromene Formation

To synthesize the starting material for this transformation (Scheme 2.7), we started with 2-allyl phenol **2.54** which we protected as a TBS ether and subjected to ozonolysis to furnish **2.55**. With the aldehyde in hand we were able to access alkyne **2.56** via a Seyfirth-Gilbert homologation.⁴⁰ We needed to re-protect the alcohol with TBSCl because of silyl cleavage in the homologation workup. From alkyne **2.56** we then synthesized vinyl iodide **2.57** using Schwartz reagent and molecular iodine. One of the two coupling partners was now complete and a simple TBS protection of allyl alcohol **2.58** furnished the second partner **2.59**. In-situ boron formation with **2.59** and 9-BBN allowed us to proceed with a palladium mediated Suzuki-Miyaura coupling⁴¹ with **2.57** followed by global deprotection to yield alcohol **2.60**. We attempted to form spiro compound **2.53** by subjecting diol **2.60** to two equivalents of DDQ but we were never able to form more than trace amounts of the spiro product.



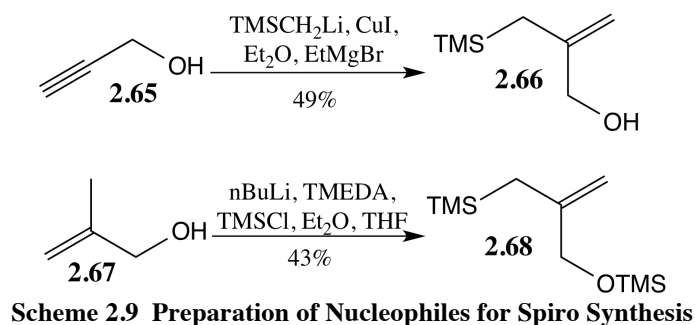
Scheme 2.7 Synthesis of Spiro Precursor

We also sought to form a spiro compound utilizing benzo[*d*][1,3]oxathiole as the starting point (Scheme 2.8). From our protocol, described previously, we obtained 2-allylbenzo[*d*][1,3]oxathiole **2.11** and we were able to oxidize the terminal alkene via a 9-BBN hydroboration to yield alcohol **2.61**. With the alcohol in hand we re-introduced our oxidative conditions to form spiro compound **2.62** within 10 minutes in 88% yield. We also performed the same transformation on the 2-(2-methylallyl)benzo[*d*][1,3]oxathiole which formed the spiro product **2.64** in 80% yield from alcohol **2.63** with minimal diastereocontrol (dr 1:1.6).

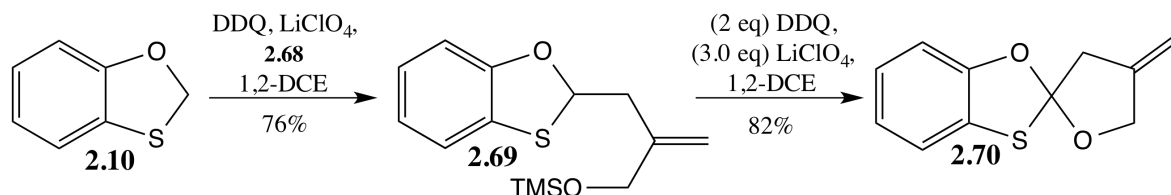


Scheme 2.8 Formation of Spiro Compounds

In order to make this process more convergent we prepared a variant of our allyl TMS nucleophile, compound **2.66**, which already had the alcohol functionality in place. This was achieved through the addition of TMSCH_2Li to propargyl alcohol **2.65**, shown in Figure 2.9.⁴²



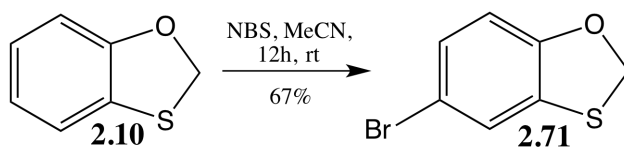
Our initial attempts failed because the alcohol proved to be the stronger nucleophile and added into the oxocarbenium first while the TMS simply fell off without addition. We altered the nucleophile by furnishing the TMS protected alcohol **2.68** via the addition of TMSCl to 2-methylprop-2-en-1-ol **2.67** after initial stirring with $n\text{-BuLi}$ (Scheme 2.9).⁴³ We used this modified nucleophile to attempt the desired addition, which went smoothly in modest yield (Scheme 2.10). After purification we subjected the product **2.69** to two equivalents of DDQ, which cleaved the TMS to furnish the free alcohol and produced the cation, allowing for the alcohol to attack and form the desired spiro compound **2.70**. This compound, which was not only surprisingly stable being in the orthoester oxidation state, now also contained a useful synthetic handle in the terminal alkene from which further derivatization could be achieved.



Encouraged by these results, we sought to develop a one-pot variation to this method. We have had moderate success in this area and have been able to furnish **2.70** via a one-pot procedure in 36% yield. We achieved these results by proceeding with the addition as usual and after 1 hour of stirring, instead of purification, we added another 3.0 equivalents of LiClO₄ and 2.4 equivalents of DDQ to furnish the cyclized product **2.70**. Further optimization is needed to make this reaction preferable to the two-step method but the current results are promising.

2.4 EXPLORING SUBSTRATE SCOPE

With the results of our nucleophile study in hand we sought to expand the scope of substrates that can be affected by these conditions. We first adjusted the electronics of our system by brominating **2.10** with NBS to yield compound **2.71**. Bromination of this compound



Scheme 2.11 Preparation of Brominated Derivative

strengthened the methylene C-H bond by destabilizing the resulting cationic intermediate. Compound **2.71** required 1.5 hours at 50°C to form the cation intermediate but, after cooling back to room temperature, subsequent nucleophilic addition was typically complete within five minutes of the nucleophile entering the reaction mixture.

The reactivity of the intermediate was increased to the point that we were able to couple it with the aryl trifluoroborate nucleophile, which provided no desired product with the standard

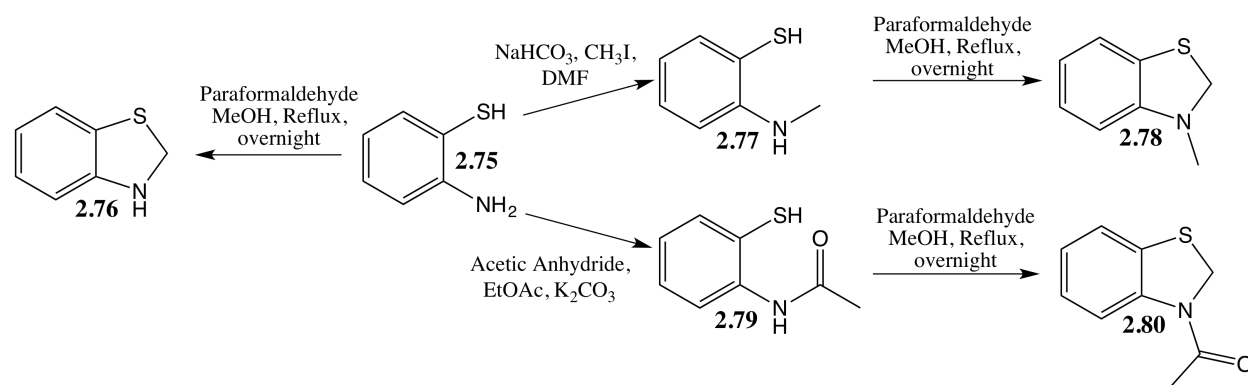
system (Table 2.2, final entry), to form compound **2.74**. A representative nucleophile from each class was tested with this substrate and we saw increased yield in every example. The complete results of addition of the representative nucleophiles into this brominated derivative are outlined in Table 2.2, below.

Table 2.3 Results of Oxidative Coupling to Brominated Substrate

| Nucleophile | Product | Yield |
|-------------|-------------|------------------|
| 2.35 | 2.72 | 91% |
| 2.36 | 2.72 | 84% |
| 2.24 | 2.73 | 79% 1.3:1 dr |
| 2.34 | 2.74 | 30% ^a |

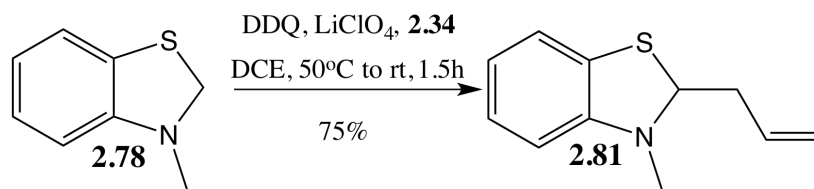
All reactions run in 1,2-DCE with LiClO₄ (1.5 eq) and DDQ (1.2 eq). Reactions stirred with DDQ for 1 hour at 50°C prior to adding nucleophile (1.2 eq). Reaction mixtures purified after stirring an additional 20 minutes. ^aReactions stirred overnight.

We proceeded to synthesize and examine N-substituted derivatives of these compounds to see if we could activate the methylene protons toward oxidation (Scheme 2.12). To substitute the oxygen in the ring with nitrogen we began with 2-aminothiophenol **2.75** and cyclized with paraformaldehyde to yield **2.76**.⁴⁴ The N-methylated derivative **2.78** was accessed by adding iodomethane⁴⁵ to **2.75** and then cyclizing the product in the same manner as before. Finally we prepared the acylated derivative by acylation of **2.75**, followed by cyclization to **2.80**.⁴⁴



Scheme 2.12 Preparation of Nitrogen Containing Rings

We were unable to oxidize **2.76** and **2.80** to the desired cation but we were able to furnish coupled product **2.81** using allyl tributyl stannane and benzothiazoline **2.78** (Scheme 2.13). Unfortunately after our initial success forming **2.81** we found that the weaker allyl silane and borane nucleophiles were unreactive with **2.78**. These initial results are promising and further study should result in more successful couplings with this substrate.



Scheme 2.13 Coupling with N-methylated Substrate

2.5 CONCLUSIONS

Herein we have reported a method to form C-2 substituted benzannulated 5 membered ring systems via an oxidative coupling procedure. This method provides a more economical option for accessing these types of compounds than previously available and allows for reaction with a broad range of nucleophiles.

A good next step would be to further analyze the reactions that produced diastereomers. Determining diastereomeric ratio is a good initial finding and helps better understand these reactions but this is just scratching the surface of what can be learned. Elucidating exactly which diastereomer we have in excess could be achieved through X-ray analysis of a resultant compound. All of our additions that resulted in diastereomers, however, were oils therefore we would first need to produce a crystallized derivative. This could be achieved by first shortening the carbon chain that we produce from our initial addition, which tends to lead to oil products. Additionally, the introduction of a large flat moiety onto the molecule will help to induce crystallization by allowing a more flat structure to form. With a crystal structure of our compound we could determine absolute stereochemistry and from that postulate the manner in which the nucleophile actually attacks the cation.

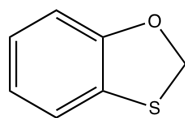
Further study will also include expanding the scope of the substrates that undergo these transformations both by synthesizing additional heterocycles and by altering conditions to make unreactive or minimally reactive cations that were formed more labile. Additionally improving the yield of the one-pot spiro forming reaction will help make this method a more attractive option in synthetic schemes. Another area worth exploring is in developing an asymmetric variant, potentially utilizing a chiral phosphoric acid catalyst in place of LiClO_4 .

APPENDIX A

SUPPORTING INFORMATION

General Experimental Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, Bruker Avance 400 spectrometer at 400 MHz and 100 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peaks was used as a reference value, for ^1H NMR: $\text{CDCl}_3 = 7.26$ ppm, for ^{13}C NMR: $\text{CDCl}_3 = 77.0$. Data are reported as follows: (s = singlet; d = doublet; t = triplet, q = quartet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dt = doublet of triplet; br = broad; app = apparently). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2 . Optical rotations were measured on a Perkin-Elmer 241 polarimeter with sodium lamp at ambient temperature as follows: $[\alpha]_D^{25}$ (c, g/100 mL). Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride, acetonitrile, and benzene were distilled under N_2 from CaH_2 . Analytical TLC was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or

flame-dried glassware under a positive pressure of N₂ with magnetic stirring unless otherwise noted. Alkylolithium reagents were titrated using menthol and the indicator 2,2-dipyridyl in THF prior to use.

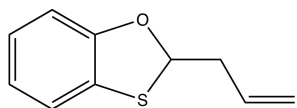


benzo[d][1,3]oxathiole (2.10): Dibromomethane (5.01mL, 59.4mmol) and Adogen 464 (1.21g, 2.77mmol) were added to a flask of refluxing H₂O (15mL). A solution of 2-mercaptophenol (5.0g, 39.6mmol) and NaOH (3.96g, 99.1mmol) in H₂O (18mL) was added over 4.5 hours. After addition was complete, the reaction mixture was stirred while refluxing for an additional 5 hours. The solution was allowed to cool to room temperature and poured into H₂O after which it was extracted with EtOAc (5x 25mL). The organic layer was dried over MgSO₄, concentrated under reduced pressure, and purified via flash chromatography (SiO₂, 4:1 Pentane:Et₂O) to yield **2.10** as a clear oil (2.91g, 53.2% yield): ¹HNMR (300MHz, CDCl₃) 7.18 (dd, 1H, *J*=10.0, 1.6Hz), 7.00 (td, 1H, *J*=10.0, 1.6Hz), 6.88 (td, 1H, *J*=10.0, 1.6), 6.83 (dd, 1H, *J*=10.0, 1.2Hz), 5.68, (s, 1H); ¹³CNMR (125 MHz, CDCl₃) 156.4, 126.2, 126.0, 122.7, 122.6, 110.6, 75.3; IR(neat) 3066, 2925, 2871, 1468, 1450, 1326, 1208, 744 ;HRMS (ESI): *m/z* calcd for C₇H₆O₇S [M]⁺ 138.0139, found 138.0136

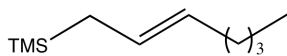
General Procedure for Oxidative Coupling

To a solution of benzoxathiole (1.0 equiv.) in DCE (0.1M) is added LiClO₄ (1.5 equiv.) and DDQ (1.2 equiv.). The reaction mixture is stirred until complete starting material consumption is indicated by TLC analysis. The nucleophile (1.2 equiv.) is then added and the reaction is

stirred until addition is complete (monitored via TLC). The reaction is then concentrated and purified directly via flash chromatography.

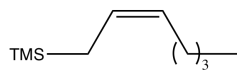


2-allylbenzo[d][1,3]oxathiole (2.11): The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (200mg, 1.45 mmol), LiClO₄ (231mg, 2.17 mmol), 4 Å MS (200mg), DDQ (395mg, 1.74mmol), and DCE (14mL). After 30 min the oxidation was complete and allyltributyl stannane (0.67mL, 2.17 mmol) was added. The reaction was stirred for 1 hour after which it was purified directly via flash chromatography (SiO₂, Pentane) to give **2.11** as a clear oil (232mg, 90% yield): ¹HNMR (400MHz, CDCl₃) 7.12 (dd, 1H, *J*=7.6, 1.2Hz), 6.99 (td, 1H, *J*=7.6, 1.2Hz), 6.87 (td, 1H, *J*=7.6, 0.8Hz), 6.80 (dd, 1H, *J*=8.0, 0.8Hz), 6.09 (t, 1H, *J*=6.4Hz), 5.86 (ddt, 1H, *J*=24.0, 10.0, 6.8Hz), 5.23 (dd, 1H, *J*=17.2, 1.2Hz), 5.19 (dd, 1H, *J*=10.0, 1.2Hz), 2.85-2.92 (m, 1H), 2.70-2.77 (m, 1H); ¹³CNMR (100 MHz, CDCl₃) 155.9, 132.1, 126.0, 125.8, 122.5, 122.3, 119.4, 110.5, 89.7, 41.7; IR (neat) 3074, 2978, 2973, 2903, 1463, 1213, 745 HRMS (ESI): *m/z* calcd for C₁₀H₁₀OS [M+H]⁺ 179.0486, found 179.0549

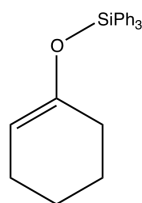


(E)-hept-2-en-1-yltrimethylsilane (2.20): To a flask containing (*E*)-1-Iodohept-1-ene (2459mg, 11.71 mmol) in dry, degassed THF (35 mL) at 0 °C was added Pd(PPh₃)₄ (339mg, 0.293mmol) and a 1.0 M solution of (trimethylsilyl)methylmagnesium chloride in diethyl ether (15.22mL). After 2 h, the reaction was quenched with H₂O (15mL) and a saturated solution of NH₄Cl. The aqueous layer was extracted with hexanes (3x 20mL), dried over MgSO₄, and concentrated under vacuum. The crude residue was purified using flash

chromatography (SiO₂, 100% hexanes) to yield the silane **2.20** as a clear oil (1596mg, 80% yield): ¹HNMR (400MHz, CDCl₃) 5.33-5.40 (m, 1H), 5.20-5.27 (m, 1H), 1.97 (d, 2H, *J*=4.2Hz), 1.39 (d, 2H, *J*=5.7), 1.25-1.36 (m, 4H), 0.88 (t, 3H, *J*=4.8Hz) 0.20 (s, 9H); *These values are consistent with literature values.*³²

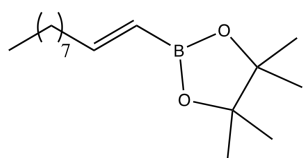


(Z)-hept-2-en-1-yltrimethylsilane (2.22): To a flask containing sodium borohydride (52mg, 1.36 mmol) in ethanol (4.5mL) was added a 1.0 M aqueous solution of NaOH (05mL). This solution was sonicated for 5 min and the remaining solids were filtered away. This NaBH₄ solution was then added to a flask containing Ni(OAc)₂·4H₂O in ethanol (95mL). After stirring for 5 min, ethylenediamine (0.192mL, 2.87 mmol) was added. After stirring for an additional 5 min, 1-(Trimethylsilyl)-hept-2-yne (1207mg, 7.17 mmol) was added and the N₂ atmosphere was replaced with an H₂ atmosphere using a balloon. The reaction mixture stirred vigorously for 3 h and was then quenched with H₂O (100mL). The solution was extracted with hexanes (3x 50mL), dried over MgSO₄, and was concentrated under vacuum. The crude residue was purified using flash chromatography (SiO₂, 2% diethyl ether in pentanes) to yield the silane (1059mg, 87% yield): ¹HNMR (400MHz, CDCl₃) 5.34-5.42 (m, 1H), 5.23-5.30 (m, 1H), 1.95-2.01 (m, 2H), 1.46 (d, 2H, *J*=8.4), 1.29-1.35 (m, 2H), 0.90 (t, 3H, *J*=5.4), 0.01 (s, 9H) *These values are consistent with literature values.*³³



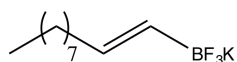
(cyclohex-1-en-1-yloxy)triphenylsilane (2.24): Cyclohexanone (3g, 30.57 mmol), Et₃N (7.42g, 73.36 mmol), and DMF (2mL) combined and cooled to 0°C. PhSiCl (10.82g, 36.68

mmol) in 2mL DMF added dropwise over 1 hour. Reaction mixture was then heated to 110°C and stirred overnight after which it was cooled to room temperature and poured over NaHCO₃. Vacuum concentration followed by flash column purification (SiO₂, 10% EtOAc in Hexanes) yielded **2.24** as a clear oil product (2.27g, 82% yield): ¹HNMR (500MHz, CDCl₃) 6.64 (dd, 6H, *J*=8.0, 1.5Hz), 6.44 (tt, 3H, 7.0, *J*=1.5Hz), 7.37 (t, 6H, *J*=7.5Hz), 4.91-4.94 (m, 1H), 1.99-2.03 (m, 2H), 1.87-1.91 (m, 2H), 1.54-1.59 (m, 2H), 1.39-1.44 (m, 2H) *These values are consistent with literature values.*³⁴



(*E*)-2-(dec-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.86):

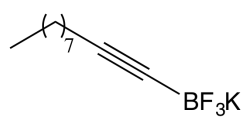
To a solution of 1-decyne (**2.30**) (1.00 g, 7.39 mmol) in CH₂Cl₂ (3.6 mL) at 0 °C was added pinacolborane (0.972 g, 7.59 mmol) and HZrCp₂Cl (0.093 g, 0.362 mmol). The solution was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic layer was dried over MgSO₄ and concentrated under vacuum. The crude residue was purified using flash chromatography (1% to 5% diethyl ether in hexanes) to yield borane **2.86** (1.50 g, 78%): ¹HNMR (CDCl₃, 300 MHz) δ 6.63 (dt, 1H, *J* = 18.0, 6.3 Hz), 5.42 (d, 1H, *J* = 18.0 Hz), 2.16 (q, 2H, *J* = 6.6 Hz), 1.35-1.46 (m, 2H), 1.26 (m, 22H), 0.87 (t, 3H, *J* = 6.3 Hz). *These data are consistent with literature values.*³⁸



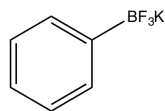
Potassium (*E*)-dec-1-enyltrifluoroborate (2.31):

To a solution of borane **2.86** (1.50 g, 5.63 mmol) in acetonitrile (14 mL) was added KHF₂ (1.55 g, 19.9 mmol) and H₂O (4.6 mL). The solution was stirred for 2 h and was concentrated. The resulting solid was

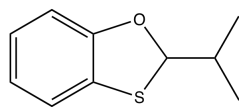
dissolved in hot acetone and filtered to remove undesired salts. The filtrate was concentrated and taken up in minimal volume of hot acetone to dissolve the solid completely. Adding diethyl ether to the solution solidified the desired product. The solid was collected by vacuum filtration to yield **2.31** (0.831 g, 60%): ^1H NMR (DMSO- d_6 , 400 MHz) δ 5.44 (dt, 1H, J = 16.8, 6.0 Hz), 5.15-5.22 (m, 1H), 1.85 (q, 2H, J = 6.0 Hz), 1.22-1.32 (m, 12H), 0.85 (t, 3H, J = 6.0 Hz). *These data are consistent with literature values.*³⁸



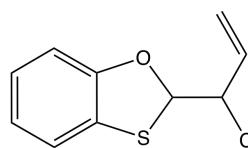
potassium dec-1-yn-1-yltrifluoroborate (2.32) To a solution of 1-decyne (**2.30**) (1.50 g, 10.8 mmol) in THF (23 mL) at $-78\text{ }^{\circ}\text{C}$ was added a 1.6 M solution of *n*-butyllithium in hexanes (6.8 mL, 10.8 mmol) drop wise. After 1 h, trimethyl borate (1.8 mL, 16.2 mmol) was added. The solution was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$ and warmed to $0\text{ }^{\circ}\text{C}$ where it was stirred for an additional hour. KHF_2 (5.05 g, 65 mmol) was added via H_2O (5 mL) slowly. The solution was stirred for 1 h at $0\text{ }^{\circ}\text{C}$ and warmed to rt where it was stirred for an additional hour before being concentrated under reduced pressure. The crude solid was placed under high vacuum for 16 hours. The resulting solid was dissolved in hot acetone and filtered to remove undesired salts. The filtrate was concentrated and taken up in a minimal volume of hot acetone to dissolve the solid completely. Adding diethyl ether to the solution solidified the desired product. The solid was collected by vacuum filtration to yield **2.32** (1.87g, 71% yield): ^1H NMR (300MHz, DMSO) 1.92-2.00 (m, 2H), 1.20-1.37 (m, 12H), 0.87 (t, 3H, J =6.9Hz) *These values are consistent with literature values.*³⁹



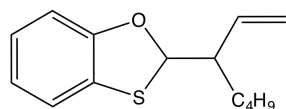
Potassium trifluoro(phenyl)borate (2.34): To a solution of phenylboronic acid (**2.33**) (3.00 g, 24.6 mmol) in methanol (7.5 mL) was added a 4.5 M aqueous solution of KHF₂ (18.8 mL, 81.9 mmol). After 30 min the reaction mixture was filtered and the solid was washed with cold acetonitrile. The collected solid was recrystallized from acetonitrile to yield the trifluoroborate salt (4.25 g, 94%): ¹H NMR (DMSO-d₆, 300 MHz) δ 7.29 (d, *J* = 6.6 Hz, 2H), 6.96-7.09 (m, 3H). *These values are consistent with literature values.*²⁴



2-(but-3-en-2-yl)benzo[d][1,3]oxathiole (2.38): The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (200mg, 1.45 mmol), LiClO₄ (233mg, 2.17 mmol), 4 Å MS (200mg), DDQ (394mg, 1.74mmol), and DCE (14mL). The reaction mixture is stirred for 30 min. after which (E)-Crotyl trimethylsilane (278mg, 2.17mmol) is added. The solution is stirred for 1 hour and then purified directly via flash chromatography (SiO₂, Pentane) to give **2.38** as a clear oil (206mg, 74% yield): ¹H NMR (400MHz, CDCl₃) 7.10 (d, 1H, *J*=7.6Hz), 6.97 (t, 1H, *J*=7.6Hz), 6.84 (t, 1H, *J*=7.6Hz), 6.78 (d, 1H, *J*=8.0Hz), 6.00 (d, 0.83H, *J*=6.0Hz), 5.94 (d, 0.17H, *J*=6.4Hz), 5.85 (m, 1H), 5.18 (m, 2H), 2.85 (p, 1H, *J*= 13.2, 6.8, 6.4Hz), 1.21 (d, 0.70H, *J*=6.8Hz), 1.17 (d, 2.3H, *J*=6.8Hz); ¹³C NMR (125 MHz, CDCl₃) 156.2, 138.0, 137.9, 125.6, 125.6, 122.1, 121.9, 121.8, 117.1, 116.6, 109.9, 94.1, 94.1, 44.4, 43.6, 43.4, 15.8, 14.7; IR (neat) 3071, 2974, 2931, 2875, 1640, 1577, 1464, 1206, 1021, 999, 922, 743; HRMS (ESI): *m/z* calcd for C₁₁H₁₃OS [M+H]⁺ 193.0609, found 192.0691

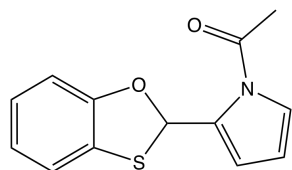


2-(hept-1-en-3-yl)benzo[d][1,3]oxathiole (2.39): The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), LiClO₄ (116mg, 1.09 mmol), 4 Å MS (103mg), DDQ (196mg, 0.868 mmol), and DCE (7mL). The reaction mixture is stirred for 30 min. after which (*E*)-hept-2-en-1-yltrimethylsilane (**2.20**) (148mg, 0.868 mmol) is added. The solution is stirred for 4 h and then purified directly via flash chromatography (SiO₂, Hexanes) to give **2.39** (3.1:1 dr) as a clear oil (122mg, 72%yield). ¹HNMR (400MHz, CDCl₃) 7.10 (dd, 1H, *J* = 7.6, 1.2 Hz), 6.97 (td, 1H, *J* = 7.6, 1.2 Hz), 6.84 (td, 1H, *J* = 7.6, 1.2 Hz), 6.77 (dd, 1H, *J* = 8.0, 0.8 Hz), 6.02 (d, 0.76H, *J* = 5.6 Hz), 5.99 (d, 0.26H, *J* = 6.8Hz), 5.61-5.71 (m, 1H), 5.14-5.23 (m, 2H), 2.54-2.64 (m, 1H), 1.58-1.68 (m, 1H), 1.30-1.45 (m, 5H), 0.89 (t, 3H, *J* = 6.9 Hz); ¹³CNMR (100MHz, CDCl₃) 156.12, 136.9, 125.6, 122.1, 121.9, 121.8, 118.4, 110.0, 93.4, 50.3, 29.6, 29.1, 22.6, 14.0; IR (neat) 3073, 2956, 2929, 2859, 1577, 1464, 1209, 1119, 920, 743; HRMS (ESI): *m/z* calcd for C₁₄H₁₉OS [M+H]⁺ 235.1078, found 235.1150



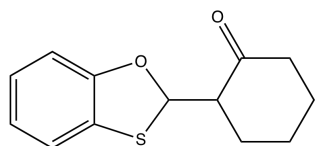
2-(hept-1-en-3-yl)benzo[d][1,3]oxathiole (2.40): The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), LiClO₄ (116mg, 1.09 mmol), 4 Å MS (103mg), DDQ (196mg, 0.868 mmol), and DCE (7mL). The reaction mixture is stirred for 30 min. after which (*Z*)-hept-2-en-1-yltrimethylsilane (**2.22**) (149mg, 0.868 mmol) is added. The solution is stirred for 4 h and then purified directly via flash chromatography (SiO₂, Hexanes) to give **2.40** (1:4.6 dr) as a clear oil (112mg, 66%yield): ¹HNMR (400MHz, CDCl₃) 7.10 (d, 1H, *J* = 7.6 Hz), 6.96 (t, 1H, *J* = 7.6 Hz), 6.84 (t, 1H, *J* = 7.6

Hz), 6.76 (d, 1H, J = 8.0 Hz), 6.01 (d, 0.18H, J = 6.8 Hz), 5.99 (d, 0.82H, J = 6.8 Hz), 5.62-5.72 (m, 1H), 5.14-5.24 (m, 2H), 2.60-2.72 (m, 1H), 1.24-1.43 (m, 6H), 0.90 (t, 3H, J = 6.4 Hz); ^{13}C NMR (100MHz, CDCl_3) 156.3, 136.6, 125.8, 125.6, 122.0, 121.8, 118.8, 110.0, 93.5, 50.5, 30.2, 29.1, 22.6, 14.0; IR (neat) 3073, 2956, 2929, 2859, 1762, 1577, 1464, 1209, 1119, 920, 743; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{19}\text{OS}$ $[\text{M}+\text{H}]^+$ 235.1078, found 235.1154



1-(2-(benzo[*d*][1,3]oxathiol-2-yl)-1*H*-pyrrol-1-yl)ethan-1-one (2.41):

The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), LiClO_4 (115mg, 1.09 mmol), 4 Å MS (100mg), DDQ (197mg, 0.868 mmol), and DCE (7mL). The reaction mixture is stirred for 30 min. after which 1-(1-((trimethylsilyl)oxy)vinyl)-1*H*-pyrrole (158mg, 0.868 mmol) is added. The solution is stirred for 4 h and then purified directly via flash chromatography (SiO_2 , 10% EtOAc in Hexanes) to give **2.41** as a white oil (78mg, 44%yield). ^1H NMR (300MHz, CDCl_3) 7.46 (s, 1H), 7.07-7.11 (m, 2H), 7.02 (td, 1H, J = 7.2, 1.2Hz), 6.92 (dd, 1H, J = 8.1, 1.2Hz), 6.87 (dt, 1H, J = 7.5, 1.2Hz), 6.38-6.41 (m, 1H), 6.20 (t, 1H, J = 3.3Hz), 2.57 (s, 3H); ^{13}C NMR (100MHz, CDCl_3) 169.4, 156.2, 135.0, 125.7, 124.8, 122.5, 122.2, 121.6, 112.5, 112.4, 110.1, 84.3, 23.4; IR (neat) 3146, 1205, 1056, 1720, 1464, 1366, 1302, 1173, 1124, 1031, 952, 828, 741; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 246.0589, found 246.0583; Melting Point 153°C



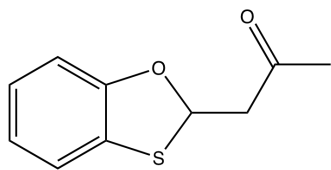
2-(benzo[d][1,3]oxathiol-2-yl)cyclohexanone (2.42) The general

procedure for oxidative coupling was followed using benzoxathiole **2.10** (125mg, 0.908 mmol), LiClO₄ (145mg, 1.36 mmol), 4 Å MS (100mg), DDQ (245mg, 1.09 mmol), and DCE (10mL).

The reaction mixture is stirred for 30 min. after which (cyclohex-1-en-1-yloxy)triphenylsilane (357mg, 1.09 mmol) is added. The solution is stirred for 1 hour and then purified directly via flash chromatography (SiO₂, Hexanes) to give **2.42** (1.2:1 dr) as a clear oil (126mg, 64% yield):

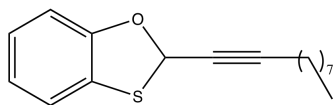
(major diastereomer) ¹HNMR (400MHz, CDCl₃) 7.10 (dd, 1H, *J*=7.6, 1.6Hz), 6.96 (td, 1H, *J*=7.6, 1.6Hz), 6.84 (td, 1H, *J*=7.6, 1.2Hz), 6.77 (dd, 1H, *J*=7.6, 1.2Hz), 6.13 (d, 1H, *J*=8.0Hz), 2.95-3.02 (m, 1H), 2.56-2.62 (m, 1H), 2.43-2.49 (m, 1H), 2.34-2.38 (m, 1H), 2.09-2.16 (m, 1H), 1.92-1.99 (m, 1H), 1.66-1.72 (m, 2H), 1.53-1.61 (m, 1H); ¹³CNMR (100 MHz, CDCl₃) 210.5, 155.4, 126.1, 125.5, 122.2, 121.7, 110.1, 87.9, 58.2, 42.3, 30.5, 27.8, 24.6; IR (neat) 3068, 3021, 2935, 2861, 1708, 1576, 1464, 1203, 1118, 920, 886, 840, 744; HRMS (ESI): *m/z* calcd for C₁₃H₁₄O₂S [M]⁺234.0715, found 234.0723

(minor diastereomer) ¹HNMR (400MHz, CDCl₃) 7.09 (dd, 1H, *J*=7.6, 1.6Hz), 6.95 (td, 1H, *J*=7.6, 1.6Hz), 6.83 (td, 1H, *J*=7.6, 1.2Hz), 6.75 (dd, 1H, *J*=7.6, 1.2Hz), 6.47 (d, 1H, *J*=4.8Hz), 3.08-3.15 (m, 1H), 2.43-2.49 (m, 1H), 2.32-2.39 (m, 1H), 2.18-2.24 (m, 1H), 2.06-2.13 (m, 1H), 1.91-1.97 (m, 1H), 1.78-1.87 (m, 1H), 1.64-1.74 (m, 2H); ¹³CNMR (100 MHz, CDCl₃) 210.2, 156.1, 125.8, 125.5, 122.0, 121.6, 109.8, 88.6, 56.0, 42.2, 27.5, 27.3, 24.2; IR (neat) 3068, 3021, 2935, 2861, 1708, 1576, 1464, 1203, 1118, 920, 886, 840, 744; HRMS (ESI): *m/z* calcd for C₁₃H₁₄O₂S [M]⁺234.0715, found 234.0692



1-(benzo[d][1,3]oxathiol-2-yl)propan-2-one (2.43):

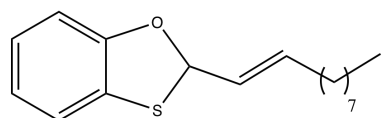
The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), LiClO₄ (115mg, 1.09 mmol), 4 Å MS (100mg), DDQ (197mg, 0.868 mmol), and DCE (7mL). The reaction mixture is stirred for 30 min. after which triisopropyl(prop-1-en-2-yloxy)silane (**2.29**) (186mg, 0.868 mmol) is added. The solution is stirred for 1 hour and then purified directly via flash chromatography (SiO₂, 10% to 20% EtOAc in Hexanes) to give **2.43** as a white solid (38mg, 27%yield). ¹HNMR (400MHz, CDCl₃) 7.13 (d, 1H, *J* = 7.2 Hz), 6.99 (t, 1H, *J* = 7.6 Hz), 6.88 (t, 1H, *J* = 7.2 Hz), 6.80 (d, 1H, *J* = 7.6 Hz), 6.36 (t, 1H, *J* = 6.0 Hz), 3.31-3.38 (dd, 1H, *J* = 17.2, 6.0 Hz), 3.07-3.15 (dd, 1H, 17.2, 7.2), 2.22 (s, 3H); ¹³CNMR (125MHz, CDCl₃) 204.6, 155.1, 125.9, 125.4, 122.5, 122.1, 110.5, 84.9, 50.9, 30.6; IR (neat) 2917, 2849, 1704, 1464, 749; HRMS (ESI): *m/z* calcd for C₁₀H₁₀O₂S [M]⁺ 294.0402, found 294.0400



2-(dec-1-yn-1-yl)benzo[d][1,3]oxathiole (2.44):

The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (200mg, 1.45 mmol), LiClO₄ (231mg, 2.17 mmol), 4 Å MS (200mg), DDQ (395mg, 1.74mmol), and DCE (14mL). The reaction mixture is stirred for 30 min. after which borane **2.32** (424mg, 1.74 mmol) is added. The solution is stirred for 1 hour and then purified directly via flash chromatography (SiO₂, Pentane) to give **2.44** as a clear oil (258mg, 65%yield). ¹HNMR (400MHz, CDCl₃) 7.13 (d, 1H, *J*=7.6Hz), 7.02 (t, 1H, *J*=7.6Hz), 6.90 (t, 1H, *J*=7.6Hz), 6.84 (d, 1H, *J*=8.0Hz), 6.54 (s, 1H), 2.27 (t, 2H, *J*=7.2Hz), 1.53 (t, 2H, *J*=7.6), 1.36 (m, 2H), 1.26 (s, 10H); ¹³CNMR (100 MHz, CDCl₃) 154.8, 126.3, 125.7, 122.9, 122.2, 111.0, 90.9, 76.6, 76.0, 32.0, 29.3, 29.2, 29.0, 28.3,

22.8, 19.1, 14.3; IR (neat) 3069, 2926, 2855, 2239, 1462, 1247, 962, 743 HRMS (ESI): m/z calcd for $C_{17}H_{22}OS$ $[M]^+$ 274.1391, found 274.1374

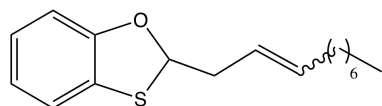


(E)-2-(dec-1-en-1-yl)benzo[d][1,3]oxathiole (2.45): The general

procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), $LiClO_4$ (115mg, 1.09 mmol), 4 Å MS (100mg), DDQ (197mg, 0.868 mmol), and DCE (7mL).

The reaction mixture is stirred for 30 min. after which potassium (*E*)-dec-1-enyltrifluoroborate (**2.29**) (214mg, 0.868 mmol) is added. The solution is stirred for 4 h and then purified directly via flash chromatography (SiO_2 , Hexanes) to give **2.45** as a clear oil (110mg, 55%yield).

1H NMR (400MHz, $CDCl_3$) 7.11 (dd, 1H, $J = 7.6, 1.2$ Hz), 6.98 (td, 1H, $J = 7.6, 1.2$ Hz), 6.86 (td, 1H, $J = 7.6, 1.2$ Hz), 6.80 (dd, 1H, $J = 8.0, 0.8$ Hz), 6.41 (d, 1H, $J = 7.2$ Hz), 5.81-5.96 (m, 2H), 2.09 (q, 2H, 6.0 Hz), 1.37-1.44 (m, 2H), 1.23-1.32 (m, 10H), 0.88 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100MHz, $CDCl_3$) 155.6, 136.6, 126.6, 126.2, 125.8, 122.3, 122.0, 110.2, 90.0, 31.9, 31.8, 29.4, 29.3, 29.2, 28.6, 22.7, 14.1; IR (neat) 3068, 2925, 2854, 1462, 1233, 1119, 1150, 1020, 960, 743; HRMS (ESI): m/z calcd for $C_{17}H_{25}OS$ $[M+H]^+$ 277.1548, found 277.1602

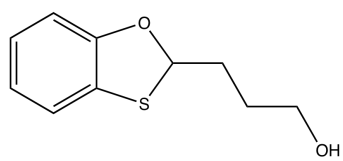


2-(dec-2-en-1-yl)benzo[d][1,3]oxathiole (2.46): The general

procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), $LiClO_4$ (114mg, 1.09 mmol), 4 Å MS (100mg), DDQ (198mg, 0.868 mmol), and DCE (7mL).

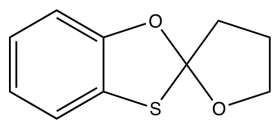
The reaction mixture is stirred for 30 min. after which potassium dec-1-en-2-yltrifluoroborate (**2.37**) (158mg, 0.868 mmol) is added. The solution is stirred for 4 h and then purified directly

via flash chromatography (SiO₂, Hexanes) to give **2.46** (2:1 olefin mixture) as a clear oil (122mg, 61%yield). ¹HNMR (400MHz, CDCl₃) 7.12 (dd, 1H, *J* = 7.5, 1.5 Hz), 6.98 (td, 1H, *J* = 7.5, 1.5 Hz), 6.86 (td, 1H, *J* = 7.5, 1.2 Hz), 6.78 (dd, 1H, *J* = 7.8, 1.2 Hz), 6.04 (t, 1H, *J* = 5.4 Hz), 5.56-5.69 (m, 1H), 5.38-5.49 (m, 1H), 2.60-2.92 (m, 2H), 1.98-2.12 (m, 2H), 1.24-1.33 (m, 10H), 0.88 (t, 3H, *J* = 6.9 Hz); ¹³CNMR (100MHz, CDCl₃) 155.8, 155.7, 135.8, 134.7, 125.8, 125.7, 125.6, 122.9, 122.2, 122.1, 122.0, 110.2, 110.16, 90.3, 90.0, 40.4, 35.1, 32.6, 31.8, 29.4, 29.3, 29.2, 29.1, 29.0, 27.7, 22.7, 14.1; IR (neat) 3068, 3011, 2924, 2854, 1577, 1463, 1240, 1211, 1119, 1021, 990, 743; HRMS (ESI): *m/z* calcd for C₁₇H₂₅OS [M+H]⁺ 277.1548, found 277.1639

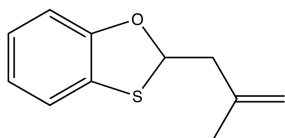


3-(benzo[d][1,3]oxathiol-2-yl)propan-1-ol (2.61): Compound **2.11**

(200mg, 1.12 mmol) is taken in THF (5 mL) and 9-BBN (145mg, 0.594 mmol) is added at room temperature. The reaction mixture is stirred for 2 hours after which it is quenched with H₂O and then cooled to 0°C. 1.25mL of NaOH (1M) and 1.25 mL of H₂O₂ (30%) are then added and stirred 30 minutes while warming to room temperature. Reaction mixture diluted with H₂O and extracted with DCM (3x 10mL), dried over MgSO₄, and concentrated under reduced pressure. Crude oil purified via flash chromatography (SiO₂, 50% Ether:Pentane mixture) to yield **2.61** as a clear oil product (174mg, 79% yield): ¹HNMR (400MHz, CDCl₃) 7.12 (dd, 1H, *J*=7.5, 1.2Hz), 6.98 (td, 1H, *J*= 7.8, 1.5Hz), 6.86, td, 1H, *J*= 7.5, 1.2Hz), 6.78 (dd, 1H, *J*= 7.8, 1.2Hz), 6.13 (t, 1H, *J*= 6.0Hz), 3.73 (q, 2H, *J*=6.0Hz), 2.14 (m, 2H), 1.79 (m, 2H), 1.37 (s, 1H); ¹³CNMR (100 MHz, CDCl₃) 155.7, 125.8, 125.7, 122.3, 122.1, 110.2, 90.2, 62.3, 33.62, 28.4; IR (neat) 3345, 3067, 2945, 2877, 1576, 1463, 1208, 1058, 942, 745; HRMS (ESI): *m/z* calcd for C₁₀H₁₁O₂S [M-H]⁺ 195.0558, found 195.0449

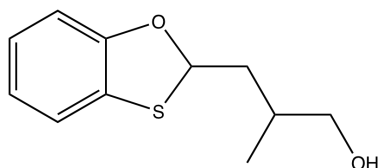


4',5'-dihydro-3'*H*-spiro[benzo[*d*][1,3]oxathiole-2,2'-furan] (2.62): To a solution of **2.61** (174mg, 0.887 mmol) in DCM (8 mL) is added LiClO₄ (142mg, 1.33 mmol) and DDQ (242mg, 1.06 mmol). The reaction mixture is stirred for 30 min after which it is purified directly via flash chromatography (SiO₂, Pentane) to give **2.62** as a pale yellow oil (152mg, 88%yield): ¹HNMR (500MHz, C₆D₆) 6.92 (dd, 1H, *J*=8.0,1.0Hz), 6.81 (dd, 1H, *J*=8.0, 1.0Hz), 6.75 (td, 1H, *J*=8.0, 1.0Hz), 6.65 (td, 1H, *J*=7.5, 1.0Hz), 3.77 (ddd, 1H, *J*=4.5, 3.5Hz), 3.57 (q, 1H, *J*=7.5Hz), 2.35 (ddd, 1H, *J*=8.0, 4.0Hz), 1.99 (dt, 1H, *J*=10.0, 1.2Hz), 1.62-1.71 (m, 1H), 1.27-1.34 (m, 1H) ¹³CNMR (125 MHz, C₆D₆) 154.4, 126.5, 126.3, 126.0, 123.0, 122.4, 111.1, 70.1, 39.7, 24.8; IR (neat) 3067, 2957, 2893, 1578, 1463, 1246, 1041, 912, 852, 745. HRMS (ESI): *m/z* calcd for C₁₀H₁₀O₂S [M]⁺ 194.0402, found 194.0331



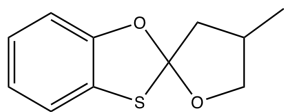
2-(2-methylallyl)benzo[*d*][1,3]oxathiole (2.82): The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (200mg, 1.45 mmol), LiClO₄ (231mg, 2.17 mmol), 4 Å MS (200mg), DDQ (395mg, 1.74mmol), and DCE (14mL). The reaction mixture is stirred for 30 min. after which 2-methyl allyl trimethyl silane (0.38mL, 2.17mmol) is added. The solution is stirred for 1 hour and then purified directly via flash chromatography (SiO₂, Pentane) to give **2.82** as a clear oil (230mg, 83% yield): ¹HNMR (300MHz, CDCl₃) 7.13 (dd, 1H, *J*=7.8, 1.2Hz), 6.99 (td, 1H, *J*=7.8, 1.2Hz), 6.86 (td, 1H, *J*=7.6, 1.2Hz), 6.80 (dd, 1H, *J*=7.8, 0.9Hz), 6.19 (t, 1H, *J*=6.6Hz), 4.93 (s, 1H), 4.86 (s, 1H), 2.90 (dd, 1H, *J*=14.4, 6.3Hz), 2.65 (dd, 1H, *J*=14.4, 6.3Hz), 1.83 (s, 1H); ¹³CNMR (100 MHz, CDCl₃) 155.6, 140.4, 125.8, 122.3, 122.1, 114.1, 110.4, 89.01, 77.4, 45.2, 22.9; IR (neat) 3074, 2669,

2912, 1649, 1462, 1285, 1212, 744; HRMS (ESI): m/z calcd for $C_{11}H_{13}OS$ $[M]^+$ 192.0609, found 192.0624



3-(benzo[d][1,3]oxathiol-2-yl)-2-methylpropan-1-ol (2.63):

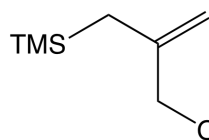
Compound **2.82** (200mg, 1.04 mmol) is taken in THF (5 mL) and 9-BBN (135mg, 0.551 mmol) is added at room temperature. The reaction mixture is stirred for 2 hours after which it is quenched with H_2O and then cooled to $0^\circ C$. 1.25mL of NaOH (1M) and 1.25 mL of H_2O_2 (30%) are then added and stirred 30 minutes while warming to room temperature. Reaction mixture diluted with H_2O and extracted with DCM (3x 10mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crude oil purified via flash chromatography (SiO_2 , 50% Ether:Pentane mixture) to yield **2.63** as a clear oil product (177mg, 81% yield): 1H NMR (400MHz, $CDCl_3$) 7.13 (dt, 1H, $J = 7.6, 1.2$ Hz), 6.99 (tt, 1H, $J = 7.2, 1.2$ Hz), 6.87 (td, 1H, $J = 7.6, 0.8$ Hz), 6.79 (dt, 1H, 8.0, 1.6), 6.17-6.23 (m, 1H), 3.57 (s, 2H), 2.27-2.34 (m, 0.5H), 1.93-2.13 (m, 2H), 1.78-1.85 (m, 0.5H), 1.46-1.51 (m, 0.5H), 1.39-1.44 (m, 0.5H), 1.03 (dd, 3H, $J = 6.8, 2.4$ Hz); ^{13}C NMR (100MHz, $CDCl_3$) 155.6, 155.5, 125.9, 125.8, 125.7, 122.3, 122.2, 122.1, 110.4, 89.3, 88.9, 77.3, 67.9, 67.7, 41.3, 40.6, 33.4, 33.2, 16.91, 16.8; IR (neat) 3379, 2921, 1462, 1210, 1022, 744; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_2S$ $[M]^+$ 210.0715, found 210.0707



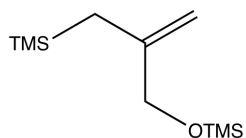
4'-methyl-4',5'-dihydro-3'H-spiro[benzo[d][1,3]oxathiole-2,2'-furan]

(2.64): To a solution of 3-(benzo[d][1,3]oxathiol-2-yl)-2-methylpropan-1-ol **2.63** (180mg, 0.856 mmol) in DCM (8 mL) is added $LiClO_4$ (137mg, 1.33 mmol) and DDQ (233mg, 1.03 mmol).

The reaction mixture is stirred for 30 min after which it is purified directly via flash chromatography (SiO₂, 10% EtOAc in Pentane) to give **2.64** as a pale yellow oil (143mg, 80%yield): ¹HNMR (300MHz, CDCl₃) 7.18 (dd, 1H, *J*=7.8, 0.9Hz), 7.03 (tt, 1H, *J*=7.8, 1.5Hz), 6.85-6.95 (m, 2H), 4.27 (t, 0.6H, *J*=7.8Hz), 4.19 (t, 0.4H, *J*=8.1Hz), 3.74 (t, 0.4H, *J*=8.4Hz), 3.64 (t, 0.6H, *J*=8.1Hz), 2.67-2.86 (m, 1.6H), 2.49-2.60 (m, 0.4H), 2.41 (dd, 0.4H, *J*=13.5, 6.9Hz), 2.14 (dd, 0.6H, *J*=13.2, 9.3), 1.21 (d, 1.1H, *J*=6.6Hz), 1.14 (d, 1.9H, *J*=6.6Hz); ¹³CNMR (100MHz, CDCl₃) 153.1, 153.0, 126.0, 125.6, 125.5, 124.6, 124.5, 122.4, 122.3, 121.6, 110.4, 110.3, 76.4, 76.1, 47.0, 46.7, 32.8, 32.3, 17.5, 16.9; IR (neat) 3067, 2961, 2875, 1578, 1462, 1236, 1186, 1066, 1096, 1013, 743; HRMS (ESI): *m/z* calcd for C₁₁H₁₃O₂S [M+H]⁺ 209.0558, found 209.0631;

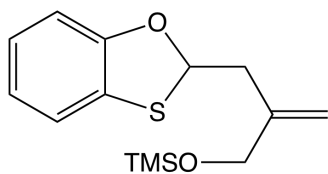


2-((trimethylsilyl)methyl)prop-2-en-1-ol (2.66): First, Me₃SiCH₂)₂CuLi was prepared by adding Me₃SiCH₂Li (2184mg, 23.19 mmol) at -10°C to a suspension of CuI (3398mg, 17.84 mmol) in 35mL of Et₂O. Solution cooled to -20°C and a solution of EtMgBr and propargyl alcohol (prepared at -10°C) was added. Mixture stirred while warming to room temperature overnight after which it is hydrolyzed with ammonia buffer, prepared as a 1:9 sat. aqueous ammonia:NH₄Cl solution. The resulting mixture is filtered and the organic layer is dried over K₂CO₃ and distilled to afford **2.66** (1640mg, 49%yield): ¹HNMR (400MHz, CDCl₃) 4.91 (s, 1H), 4.68 (s, 1H), 3.99 (d, 2H, *J*=6.0Hz), 1.54 (s, 2H), 1.38 (t, 1H, *J*=6.0Hz), 0.03 (s, 9H) *These values are consistent with literature values.*⁴²



trimethyl((2-((trimethylsilyl)methyl)allyl)oxy)silane (2.68): 2.5M solution

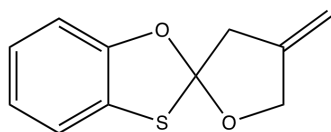
of n-BuLi (8.67mL, 13.87 mmol) taken in a flask and hexanes evaporated off. 8 mL of ether was then added to the residue and cooled to 0°C while TMEDA (2.29mL, 15.25 mmol) was added. 2-methyl allyl alcohol (0.583 mL, 6.93 mmol) was added over 15 min and the THF (4mL) was added. The solution was stirred while warming to room temperature overnight. Resulting dark red solution cooled to -78°C and freshly distilled TSMCl (3.69mL, 29.11 mmol) added quickly turning solution clear. Reaction mixture warmed to room temperature and became cloudy. Solution diluted with ether and saturated NaHCO₃ added. The organic layer was washed successively with H₂O, saturated CuSO₄ solution, H₂O, and brine. Organic layer dried over Na₂SO₄, concentrated under vacuum, and purified by distillation to yield **2.68** as a colorless oil (647mg, 43% yield): ¹HNMR (300MHz, CDCl₃) 4.91 (s, 1H), 4.63 (s, 1H), 3.95 (s, 1H), 1.49 (s, 1H), 0.13 (s, 9H), 0.22 (s, 9H) *These values are consistent with literature values.*⁴³



((2-(benzo[d][1,3]oxathiol-2-ylmethyl)allyl)oxy)trimethylsilane

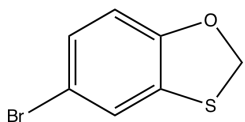
(2.69): The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), LiClO₄ (115mg, 1.09 mmol), 4 Å MS (100mg), DDQ (197mg, 0.868 mmol), and DCE (7mL). The reaction mixture is stirred for 30 min. after which trimethyl((2-((trimethylsilyl)methyl)allyl)oxy)silane (**2.68**) (188mg, 0.868 mmol) is added. The solution is stirred for 1 hour and then purified directly via flash chromatography (SiO₂, 10% EtOAc in Hexanes) to give **2.69** as a clear oil (154mg, 76%yield). ¹HNMR (300MHz, C₆D₆) 6.99 (d, 1H, *J*

= 7.6 Hz), 6.82-6.86 (m, 2H), 6.69-6.77 (m, 1H), 6.16 (t, 1H, $J = 6.3$ Hz), 5.31 (s, 1H), 5.00 (s, 1H), 4.01 (s, 2H), 2.85-2.93 (dd, 1H, $J = 14.4, 6.0$ Hz), 2.57-2.66 (dd, 1H, $J = 14.4, 6.6$ Hz), 0.17 (s, 9H); ^{13}C NMR (125MHz, C_6D_6) 156.2, 143.6, 128.3, 126.3, 126.0, 122.5, 122.3, 113.1, 110.6, 89.5, 65.7, 40.9, 0.52; IR (neat) 3072, 2956, 2899, 1464, 1251, 1211, 1112, 1074, 1021, 874, 842, 745; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{SSi}$ $[\text{M}]^+$ 280.0953, found 280.0966



4'-methylene-4',5'-dihydro-3'*H*-spiro[benzo[*d*][1,3]oxathiole-2,2'-

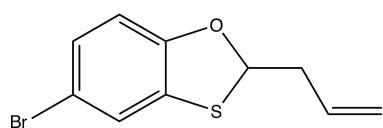
furan] (2.70): Alcohol **2.69** (150mg, 0.535 mmol) is taken in DCE (5mL) and DDQ (292mg, 1.28 mmol) added. Reaction mixture is stirred for 10 minutes and then purified directly via flash chromatography (SiO_2 , 10% EtOAc in Hexanes) to yield **2.70** as a colorless oil (91mg, 82% yield): ^1H NMR (400MHz, CDCl_3) 7.20 (d, 1H, $J = 7.6$ Hz), 7.05 (t, 1H, $J = 7.6$ Hz), 6.94 (t, 1H, $J = 7.6$ Hz), 6.90 (d, 1H, $J = 8.0$ Hz), 5.17 (t, 1H, $J = 2.4$ Hz), 5.07 (t, 1H, $J = 2.4$ Hz), 4.59-4.71 (m, 2H), 3.21-3.36 (m, 2H); ^{13}C NMR (125MHz, CDCl_3) 153.1, 142.7, 125.7, 124.7, 124.4, 122.5, 121.7, 110.6, 106.7, 72.1, 44.5; IR (neat) 3070, 2930, 2873, 1577, 1463, 1424, 1277, 1240, 1170, 1019, 960, 874, 745; HRMS (ESI): m/z calcd for $\text{C}_{11}\text{H}_{11}\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 207.0402, found 207.0472



5-bromobenzo[*d*][1,3]oxathiole (2.71): Benzoxathiole **2.10** (1.0g, 7.24

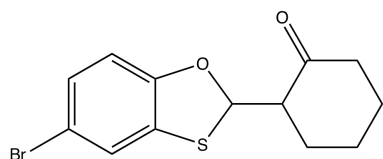
mmol) was taken in MeCN (3mL) and cooled to 0°C . NBS (1289mg, 7.24 mmol) in 3mL of MeCN added and reaction mixture heated to room temperature while stirring overnight. Reaction quenched with H_2O and hexanes added and aqueous layer extracted with 3x 5mL of

hexanes. Drying over MgSO_4 followed by vacuum concentration allowed purification via flash chromatography (SiO_2 , Hexanes) to yield **2.71** as a colorless oil (1.02g, 65% yield): ^1H NMR (500MHz, CDCl_3) 7.26 (s, 1H), 7.86 (dd, 1H, $J = 8.0, 1.5$ Hz), 6.68 (d, 1H, $J = 8.5$ Hz), 5.69 (s, 1H); ^{13}C NMR (125MHz, CDCl_3) 155.6, 128.7, 128.4, 124.8, 114.1, 111.5, 75.4; IR (neat) 3084, 2925, 2872, 1571, 1467, 1450, 1327, 1210, 1069, 998, 805, 742; HRMS (ESI): m/z calcd for $\text{C}_7\text{H}_5\text{BrOS}$ $[\text{M}]^+$ 217.9244, found 217.9219



2-allyl-5-bromobenzo[d][1,3]oxathiole (2.72): The general

procedure for oxidative coupling was followed using benzoxathiole **2.71** (200mg, 0.922 mmol), LiClO_4 (147mg, 1.38 mmol), 4 Å MS (200mg), DDQ (251mg, 1.11 mmol), and DCE (9mL). The reaction mixture is stirred for 30 min. after which borane allyltributyl stannane (0.342mL, 1.11 mmol) is added. The solution is stirred for 20 min and then purified directly via flash chromatography (SiO_2 , Pentane) to give **2.72** as a clear oil (216mg, 91%yield): ^1H NMR (500MHz, CDCl_3) 7.21 (d, 1H, $J = 2.0$), 7.07 (dd, 1H, $J = 8.5, 2.0$ Hz), 6.65 (d, 1H, $J = 8.5$ Hz), 6.10 (t, 1H, $J = 6.5$ Hz), 5.17-5.27 (m, 2H), 2.82-2.89 (m, 1H), 2.68-2.75 (m, 1H); ^{13}C NMR (125MHz, CDCl_3) 155.1, 131.5, 128.5, 128.3, 124.6, 119.6, 113.9, 111.4, 90.3, 41.4; IR (neat) 3080, 2978, 2902, 1459, 1214, 1072, 994, 925, 804, 731; HRMS (ESI): m/z calcd for $\text{C}_{10}\text{H}_9\text{BrOS}$ $[\text{M}]^+$ 255.9557, found 255.9553

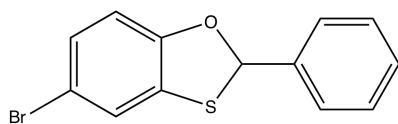


2-(5-bromobenzo[d][1,3]oxathiol-2-yl)cyclohexan-1-one (2.73):

The general procedure for oxidative coupling was followed using benzoxathiole **2.71** (100mg,

0.461 mmol), LiClO₄ (74mg, 0.691 mmol), 4 Å MS (103mg), DDQ (126mg, 0.553 mmol), and DCE (5mL). The reaction mixture is stirred for 1 hour at 50°C after which it is cooled to room temperature and (cyclohex-1-en-1-yloxy)triphenylsilane (**2.24**) (269mg, 0.553 mmol) is added. The solution is stirred for 20 minutes and then purified directly via flash chromatography (SiO₂, 10% EtOAc in Hexanes) to give **2.73** (1.3:1 dr) as a clear oil (115mg, 79%yield): (Major Diastereomer) ¹HNMR (400MHz, CDCl₃) 7.19 (s, 1H), 7.04 (dd, 1H, *J* = 8.4, 2.0 Hz), 6.62 (d, 1H, *J* = 8.4 Hz), 6.13 (d, 1H, *J* = 8.0 Hz), 2.94-3.12 (m, 1H), 2.54-2.60 (m, 1H), 2.44-2.50 (m, 1H), 2.30-2.39 (m, 1H), 1.95-1.99 (m, 1H), 1.66-1.73 (m, 2H), 1.54-1.57 (m, 2H); ¹³CNMR (100MHz, CDCl₃) 210.3, 154.7, 128.9, 128.2, 124.2, 113.8, 111.2, 88.9, 58.1, 42.2, 30.5, 27.7, 24.6; IR (neat) 3067, 2939, 2863, 1705, 1459, 1207, 1119, 996, 858, 709; HRMS (ESI): *m/z* calcd for C₁₃H₁₃BrO₂S [M]⁺ 311.9820, found 311.0814

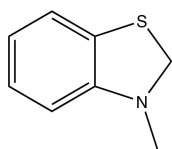
(Minor Diastereomer) ¹HNMR (400MHz, CDCl₃) 7.19 (s, 1H), 7.03 (dd, 1H, *J* = 8.4, 2.0 Hz), 6.60 (d, 1H, *J* = 8.4 Hz), 6.48 (d, 1H, *J* = 4.4 Hz), 3.08-3.15 (m, 1H), 2.45-2.50 (m, 1H), 2.32-2.40 (m, 1H), 2.10-2.22 (m, 2H), 1.63-1.88 (m, 4H); ¹³CNMR (100MHz, CDCl₃) 210.0, 155.5, 128.6, 128.3, 124.1, 113.6, 110.9, 89.5, 55.9, 42.2, 27.4, 27.1, 24.2; IR (neat) 3067, 2939, 2863, 1705, 1459, 1207, 1119, 996, 858, 709; HRMS (ESI): *m/z* calcd for C₁₃H₁₃BrO₂S [M]⁺ 311.9820, found 311.0835



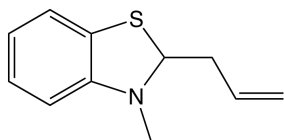
5-bromo-2-phenylbenzo[d][1,3]oxathiole (2.74): The general

procedure for oxidative coupling was followed using benzoxathiole **2.71** (100mg, 0.461 mmol), LiClO₄ (74mg, 0.691 mmol), 4 Å MS (103mg), DDQ (126mg, 0.553 mmol), and DCE (5mL). The reaction mixture is stirred for 1 hour at 50°C after which it is cooled to room temperature

and potassium trifluorophenyl borate (**2.34**) (102mg, 0.553 mmol) is added. The solution is stirred for 20 minutes and then purified directly via flash chromatography (SiO₂, Hexanes) to give **2.74** as a clear oil (41mg, 30%yield): ¹HNMR (400MHz, CDCl₃) 7.79 (s, 2H), 7.63 (s, 2H), 7.48 (d, 2H, *J* = 7.2 Hz), 7.33 (dd, 1H, *J* = 7.2, 1.2 Hz), 6.94 (dd, 1H, XX Hz), 5.93 (s, 1H); ¹³CNMR (125MHz, CDCl₃) 155.6, 154.9, 137.8, 129.7, 128.9, 128.8, 126.6, 124.8, 235.5, 225.4, 222.6, 91.2, 75.8; IR (neat) 3084, 2923, 2872, 1744, 1454, 1327, 1248, 1206, 1071, 999, 861, 740; HRMS (ESI): *m/z* calcd for C₁₃H₉BrOS [M]⁺ 291.9557, found 291.9540

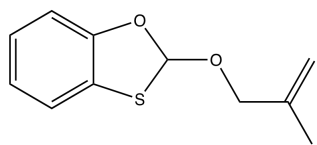


3-methyl-2,3-dihydrobenzo[d]thiazole (2.78): 2-(methylamino)benzenethiol (1.0g, 7.18 mmol) is taken in MeOH (30mL) and paraformaldehyde (280mg, 9.33 mmol) added. Reaction stirred at reflux overnight after which it was cooled to room temperature and extracted with DCM (3x 15mL) and dried over MgSO₄. Concentration followed by flash chromatography gave **2.78** as a yellow oil (650mg, 60% yield): ¹HNMR (300MHz, CDCl₃) 7.90 (dd, 1H, *J*=7.5, 0.9Hz), 7.00 (td, 1H, *J*=7.8, 1.2), 6.72 (td, 1H, *J*=7.5, 0.9Hz), 6.47 (d, 1H, *J*=7.8Hz), 4.64 (s, 1H), 2.84 (s, 1H); ¹³CNMR (100MHz, CDCl₃) 148.4, 127.2, 125.6, 122.3, 119.5, 108.1, 59.9, 36.1; IR (neat) 3204, 3056, 2951, 2860, 2803, 1583, 1482, 1452, 1360, 1110, 986, 740; HRMS (ESI): *m/z* calcd for C₈H₁₀NS [M+H]⁺ 152.0456, found 152.0538

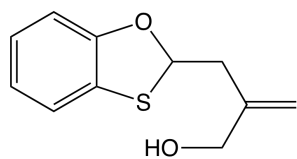


2-allyl-3-methyl-2,3-dihydrobenzo[d]thiazole (2.81): The general procedure for oxidative coupling was followed using benzothiazoline **2.78** (100mg, 0.661

mmol), LiClO₄ (106mg, 0.992 mmol), 4 Å MS (98mg), DDQ (180mg, 0.793 mmol), and DCE (6mL). The reaction mixture is stirred for 1 h at 50°C after which it is cooled to room temperature and allyltributyl stannane (0.226mL, 0.793 mmol) is added. The solution is stirred for 1 h and then purified directly via flash chromatography (SiO₂, 10% EtOAc in Hexanes) to give **2.81** as a pale yellow oil (95mg, 75% yield): ¹HNMR (500MHz, CDCl₃) 7.01 (dd, 1H, *J* = 7.5, 1.0 Hz), 6.96 (td, 1H, *J* = 7.5, 1.0 Hz), 6.65 (td, 1H, *J* = 7.5, 1.0 Hz), 6.35 (d, 1H, *J* = 7.5 Hz), 5.80-5.88 (m, 1H), 5.13-5.21 (m, 2H), 5.07 (dd, 1H, *J* = 8.5, 3.5 Hz); ¹³CNMR (125 MHz, CDCl₃) 148.3, 133.1, 125.8, 125.4, 121.6, 118.9, 118.6, 107.5, 73.8, 39.5, 34.2, 26.



2-((2-methylallyl)oxy)benzo[d][1,3]oxathiole (2.83): The general procedure for oxidative coupling was followed using benzoxathiole **2.10** (100mg, 0.723 mmol), LiClO₄ (115mg, 1.09 mmol), 4 Å MS (100mg), DDQ (197mg, 0.868 mmol), and DCE (7mL). The reaction mixture is stirred for 30 min. after which methallyl alcohol (0.073mL, 0.868 mmol) is added. The solution is stirred for 1 hour and then purified directly via flash chromatography (SiO₂, Hexanes) to give **2.83** as a clear oil (111mg, 74%yield). ¹HNMR (400MHz, CDCl₃) 7.22 (d, 1H, *J*=7.6Hz), 7.14 (s, 1H), (t, 1H, *J*=7.6Hz), 6.96 (t, 1H, *J*=7.2Hz), 6.95 (d, 1H, *J*=7.2Hz), 4.98 (s, 1H), 4.91 (s, 1H), 4.16 (d, 1H, *J*=12.4Hz), 3.98 (d, 1H, *J*=12.0Hz), 1.75 (s, 3H); ¹³CNMR (100 MHz, CDCl₃) 154.4, 140.9, 126.0, 123.9, 122.9, 122.0, 113.6, 110.6, 110.6, 69.4, 20.0; IR (neat) 3074, 2974, 2920, 2862, 1657, 1577, 1464, 1288, 1085, 959, 904, 834, 744; HRMS (ESI): *m/z* calcd for C₁₁H₁₂O₂S [M+H]⁺ 209.0636, found 209.0612



2-(benzo[d][1,3]oxathiol-2-ylmethyl)prop-2-en-1-ol (2.84): TMS Ether

2.69 (150mg, 0.535 mmol) was taken in DCE (5 mL) and DDQ (122mg, 0.535 mmol) added. Reaction mixture stirred 30 minutes and purified directly via flash chromatography (SiO₂, 10 to 20% EtOAc in Hexanes) to yield **2.84** as a clear oil (109mg, 99% yield): ¹HNMR (300MHz, CDCl₃) 7.13 (dd, 1H, *J* = 7.5, 1.2 Hz), 6.99 (td, 1H, *J* = 7.5, 1.2 Hz), 6.87 (td, 1H, *J* = 7.8, 1.2 Hz), 6.80 (dd, 1H, *J* = 7.8, 0.9 Hz), 6.23 (t, 1H, *J* = 6.3 Hz), 5.24 (s, 1H), 5.07 (s, 1H), 4.16 (s, 2H), 2.94 (dd, 1H, *J* = 14.7, 6.6 Hz), 2.72 (dd, 1H, *J* = 14.7, 6.3 Hz), 1.80 (s, 1H); ¹³CNMR (100MHz, CDCl₃) 155.3, 143.6, 125.8, 125.5, 122.3, 122.1, 114.1, 110.3, 89.0, 66.0, 40.7; IR (neat) 3344, 3072, 2918, 1652, 1577, 1463, 1210, 1065, 1021, 910, 745; HRMS (ESI): *m/z* calcd for C₁₁H₁₃O₂S [M+H]⁺ 209.0558, found 209.0641

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